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Hydrocoele of the Tunica Vaginalis—Review Article

Abstracts & Reviews

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HEPATOLENTICULAR DEGENERATION:
Preliminary Evidence For Medical Adrenalectomy In Its Treatment

Sydney Walker III, M.D.[1]

INTRODUCTION

During the past decade, the treatment of hepatolenticular degeneration (HLD, Wilson's Disease) has primarily involved the administration of various chelating agents. These drugs work to remove copper from the liver and brain, hopefully affording symptomatic relief in this almost invariably fatal disorder. British anti leucite (BAL) and especially penicillamine have brought about some temporary remissions,[1,2] but ethylene diamine tetra acetate (EDTA, versene), which is a highly potent copper chelator, is ineffective.[3] Why this therapeutic disparity should exist has not been explained by the complex research into copper and ceruloplasmin, which is the source of the rationale for the chelation therapy. In fact, the current conceptualization of HLD as a disorder of copper metabolism leaves much unexplained significant pathophysiology and clinic findings.

It was this author's feeling, given certain known effects of adrenal function, that several paradoxes could be resolved and the disease process more completely understood by investigating steroid metabolism in patients with HLD. Several clinical studies have thus been done, some of which have involved manipulation of function with drugs. This preliminary work lends encouraging evidence for the hypothesis that HLD is basically a disorder of abnormal steroid metabolism, with secondary reticuloendothelial paralysis and functional renal impairment. The possibility exists that medical adrenalectomy may be the future treatment of choice.

This paper will deal first of all with the material and thinking behind this hypothesis, then with the preliminary investigations thus far undertaken by the author, their results, significance, the questions they raise, and their implications for an entirely new therapeutic approach to HLD.

From the Division of Surgery

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BACKGROUND AND HYPOTHESIS

Repeatedly cited in the world literature, but apparently unheeded, is the striking observation of reticuloendothelial non-involvement in patients with HLD.[4] Despite increased tissue copper at the sites of the typical lesions, the scavenger elements in these organs have never been reported to show intracellular copper. In fact, the phagocytes in the liver and basal ganglia (the von Küpfer cells and microglia) do not appear to pick up any of the necrotic debris in which they wallow.

Because of these observations, it was entertained that there might be a paralysis of phagocytosis in HLD. Certain information in connection with this

possibility deserves consideration at this point. Both BAL and estrogen, which have been demonstrated to offer symptomatic relief to patients with HLD (the former has been widely used) have been shown to stimulate phagocytosis.[1,5,*] Versene, however, the chelator which has been such a perplexingly disappointing drug for HLD, has no such stimulatory ability.[3,6] The obvious question then asked is whether the effectiveness or non-effectiveness of these drugs in the treatment of HLD is basically more a function of their influence on sluggish phagocytosis than on copper binding.

Nicol and Bilbey, in their well-known work, have demonstrated that cortisone and certain other steroids work to depress phagocytic activity.[7] Could it be that the apparent paralysis of the reticuloendothelial system in HLD is secondary to a cortisone-like antiphagocytic activity?

A second paradoxical observation about HLD that stimulated speculation is the fact that little or no pathology—gross or microscopic—is found in the kidneys of these patients, yet they typically demonstrate marked functional renal impairment. There is abnormally high urinary excretion of copper, calcium, uric acid, various amino acids, and glucose, despite simultaneously normal or low serum levels of these substances.[8,9,10] Recent work has shown that normal subjects and patients with previously normal kidney function, who are given high doses of adrenocorticatropic hormone (ACTH) or glucocorticoids may also develop hypercalcuria, uricosuria, aminoaciduria, and glycosuria, in the face of similarly normal or decreased serum levels before and during drug administration.[11,12,13] The question which then emerged was whether this sort of steroid effect could also be the explanation for the gross renal dysfunction in HLD.

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*A personal communication from Prof. T. Nicol, King's College, London who has recently studied the effect of penicillamine on phagocytosis at my request, reports he has found that penicillamine has stimulating effect on the RES.

CLINICAL STUDIES

Study No. 1: Study on a single patient with HLD (patient No. 1, R.K., see appendix for case study) was first set up. This young man, who had had symptomatic Wilson's disease for a number of years, demonstrated several striking, nonspecific signs suggesting hyperadrenalism. He had labile hypertension, glycosuria, lymphopenia, osteoporosis, and the diffuse typical skin changes (with superficial vascularization) seen in Cushing's syndrome. Signs consistent with such an endocrinopathy in patients with HLD are not uncommon, and this situation, plus the questions about adrenal function already entertained in the previous section, led the investigator to anticipate biochemical evidence for increased glucocorticoid production in this patient. He was thus subjected to a standard dexamethasone suppression test,[14] in order to evaluate his adrenal status. His baseline (control) 24-hour urines, however, contained below normal 17-hydroxy- and 17-ketosteroids and normal 17-ketogenic steroids (Figure 1). After five days of adrenal suppression with dexamthasone, 0.5 mg. q.i.d., there was further depression of urinary steroid output (Figure 1). Paper chromatography was performed on the control urine and compared with the steroid pattern seen in the urine of normal subjects.[15] The urine of the HLD patient showed a heavy blue tetrazolium reducing zone of considerable intensity ($Rf = 0.2$) in an area where normal urine shows little or no discoloration, in the B-6-hydroxycorticoid range (Figure 2). This finding raised the speculation that the unusual spot on the chromatogram might represent an abnormal steroid present in patients with HLD—one which, on further investigation, would perhaps prove to be the basic substance causing the disease process. Could this abnormal steroid, not perhaps picked up in the urine by the conventional quantitative methods, explain the peculiar combination of 1) signs of adrenal hyperfunction in this patient, in association

R.K. ♂, 36		DAY 1 Control	DAY 2 Dexamethasone Suppression (8 mg)	DAY 3 Maximal Dexameth. Suppression (20mg)
PLASMA Ketogenic Steroids (μgm / 100 mL) *Normal Range 5-20μgm/100mL*	8 A.M. 8 P.M.	8.0 3.0		1.0 0.4
URINE 17-Hydroxycorticoids 17-Ketogenic Steroids 17-Ketosteroids (mg / 24 Hrs)		1.7 11.0 5.5	0.9 5.7 2.8	1.3 5.2 2.6

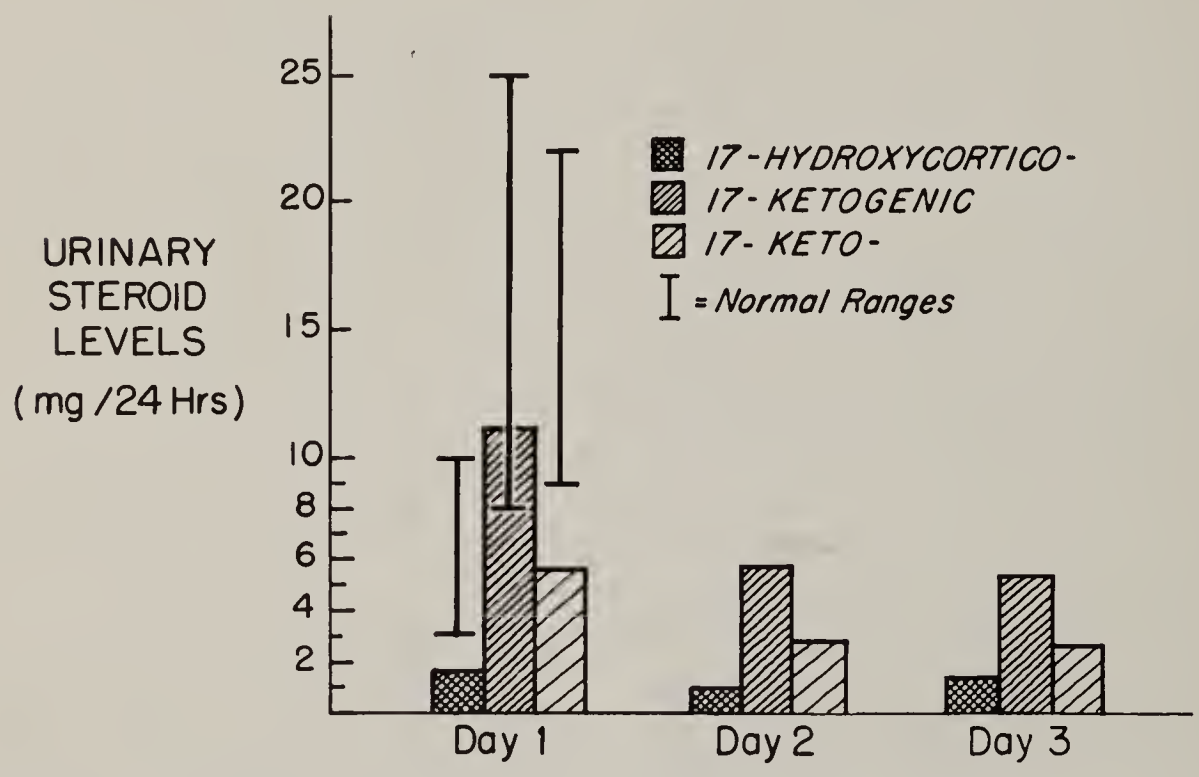

Fig. 1.—Results of Dexamethasone Suppresion Test on Steroid Levels in a Patient with Wilson's Disease.

	R.K. 36♂	R.W. 17♂	S.M. 21♀	M.G. 32♀	M.M. 17♂ (Asymptomatic)	I.S. 52♂ (Remission (?))
1. Skin Changes	+	+	+	+		
2. Osteoporosis	+			+		
3. Muscular Weakness		+	+	+		
4. Acne		+		+		
5. Hirsutism						
6. Hypertension		+				
7. Glycosuria	+		+		+	+
8. Uricosuria					+	
9. Hypercalcuria					+	
10. Leukopenia	+					

Fig. 2.—Findings Consistent with Hyperadrenal Function in 6 Patients with Hepatolenticular Degeneration.

with 2) low quantitative urinary steroid excretion, and 3) absence of signs of adrenal insufficiency?

Study No. 2: Additional studies were done on five other patients with known HLD (appendix No. 2–6) all of whom had been diagnosed by a neurologist with a special interest in this disease. At the time of this investigation, all subjects had serum and urinary copper levels consistent with HLD. In addition, four of these five also demonstrated various signs of hyperadrenalism (Figure 3). In all of them, the 24-hour

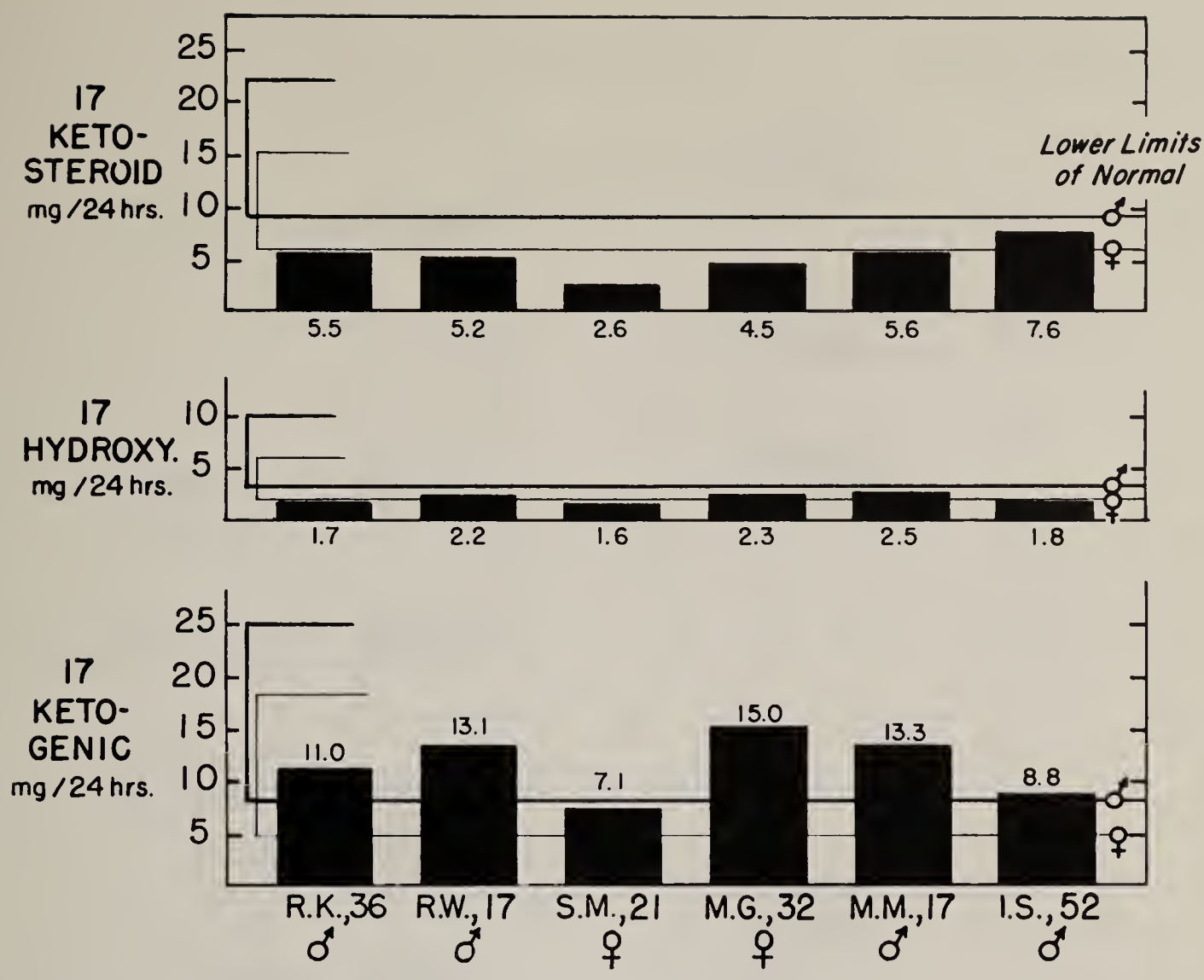

Fig. 3.—Quantitative Steroid Levels in 6 Patients with Hepatolenticular Degeneration.

urinary steroid output patterns were similar to that found in patient number 1 of the pilot study (i.e., low 17-hydroxy- and 17-ketosteroid levels, with normal to high 17-ketogenic steroid output (Figure 4). At steroid chromatography, the abnormal deposit in the B-6-hydroxycorticoid range was present in varying degrees of intensity in the urines of all of the patients except one (patient number 6), whose particular situation will be discussed later.

Study No. 3: Patients with cirrhosis are well known to develop changes in patterns of urinary steroid excretion. In order to further clarify and compare the above findings, therefore, several patients with various types of liver disease were studied to see if the above preliminary results were merely a nonspecific function of the way in which cirrhotic livers break down steroids. The urinary steroid alterations in patients with Fanconi's syndrome, alcoholic cirrhosis, and postnecrotic cirrhosis (all diagnosed by liver biopsy) were found to be of an entirely different variety than the consistent urinary steroid profile produced by patients with HLD (Figure 5). In addition, and even more impressive, is the fact that chromatographic studies on the urines failed to demonstrate any abnormal steroid deposit of the variety that had been seen in patients with HLD.

Study No. 4: Next, a study was done on three asymptomatic siblings of patients with HLD who had already died. The purpose here was to see if any urinary steroid changes would be demonstrated in people who might later develop clinical HLD. All of these subjects had normal liver profiles, and one had normal 24-hour urinary steroid output, for her age. The urine of the

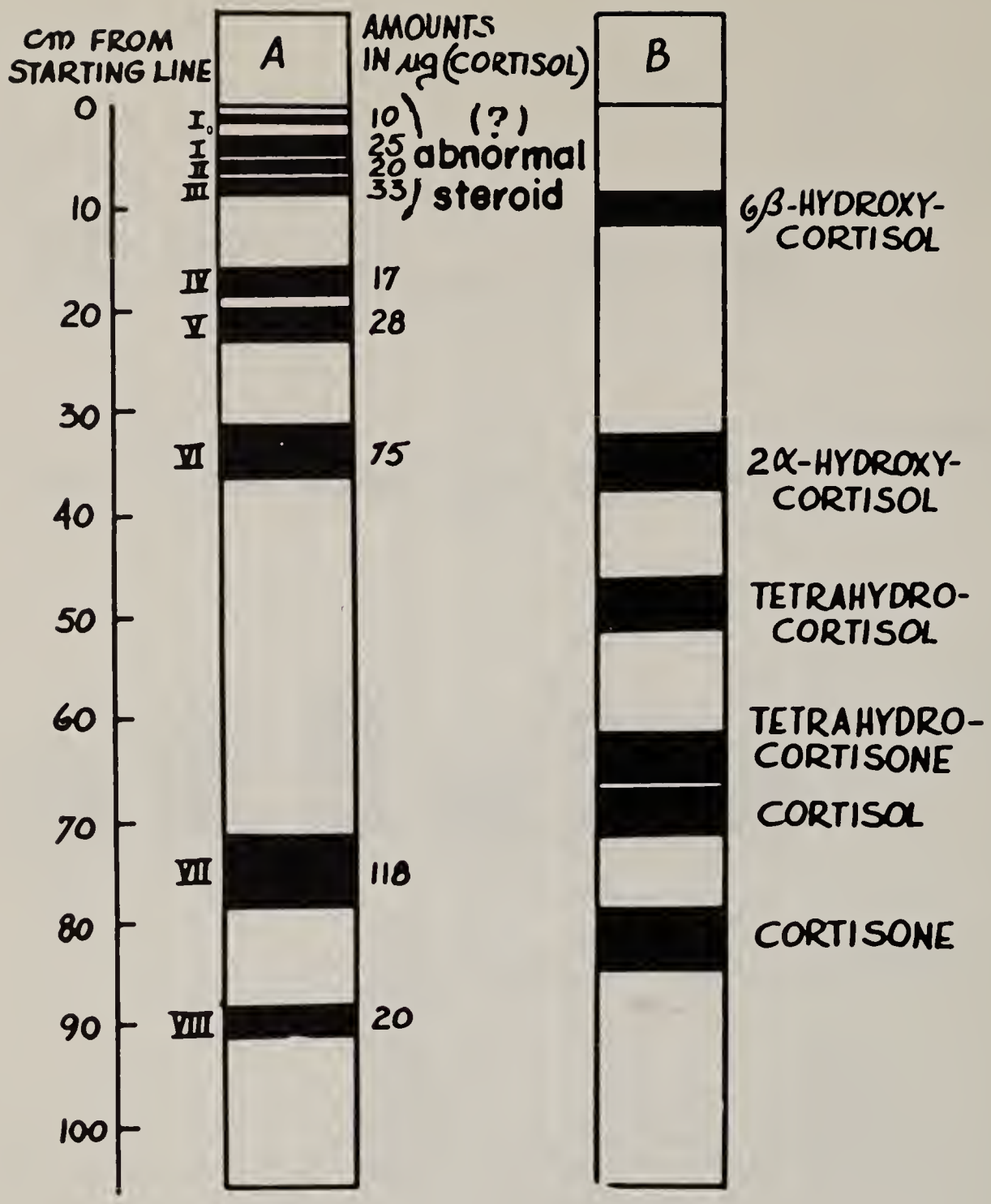

Fig. 4.—Steroid Chromatogram (from Burstein & Kimball; Analyt. Biochem., 8062)

other two children, however, showed the typical urinary steroid pattern seen in patients with full-blown HLD (Figure 6). Chromatography, as well, was done on these urines, but the results were not conclusive. A major problem in the interpretation of this chromatography, given the particular method used and its present state of development, is its lack of sensitivity. Localization and extraction of a single steroid are still crude, so that, although the definite appearance of a heavy deposit is significant, its equivocal presence, as in the strips on these children, cannot be interpreted as meaning total absence of the abnormal steroid. In order to eliminate possible bias, the chromatography in all studies was run and interpreted in a double-blind manner, and the investigator was not involved in this aspect of the work.

Study No. 5: Among the group of six patients with HLD studied and referred to earlier, one patient presented atypically from several viewpoints (patient number 6: appendix). A 52-year old male, he had been known to have HLD, heralded by psychiatric symptoms, for twenty-five years. Despite severe and characteristic earlier manifestations of

dysarthria, tremor and deranged liver function, he had not (over the past ten years) followed the typical progressive course. In fact, although he had HLD by serum and urinary copper level criteria and by certain clinical signs, he was as well at the time of investigation as he had been for some time. Of special interest to the author was the fact that this particular patient, in contrast to the others, had some signs and symptoms of adrenal insufficiency, rather than of hyperadrenalism. These included 1) low blood pressure, 2) dry and diffusely hyperpigmented skin, 3) muscular weakness, 4) easy fatiquability, and 5) a marked craving for sugar. His urinary steroid pattern was similar to that seen in the other HLD patients (Figure 4), but the abnormal deposit on chromatography appeared to be absent.

In an attempt to evaluate this patient's adrenal status, a standard ACTH stimulation test was performed.[16] He was given 80 units ACTH, intramuscullarly daily for five mornings. In response to this stimulation, there was an initial, but not striking, rise of urinary steroid output which plateaued by the fourth day and had begun to decrease on day 5 (Figure 7). This abnormal type of response could be consistent with what happens in secondary adrenal insufficiency, but a cortisol secretion test would be necessary to substantiate this diagnosis.[17] By way of comparison, are

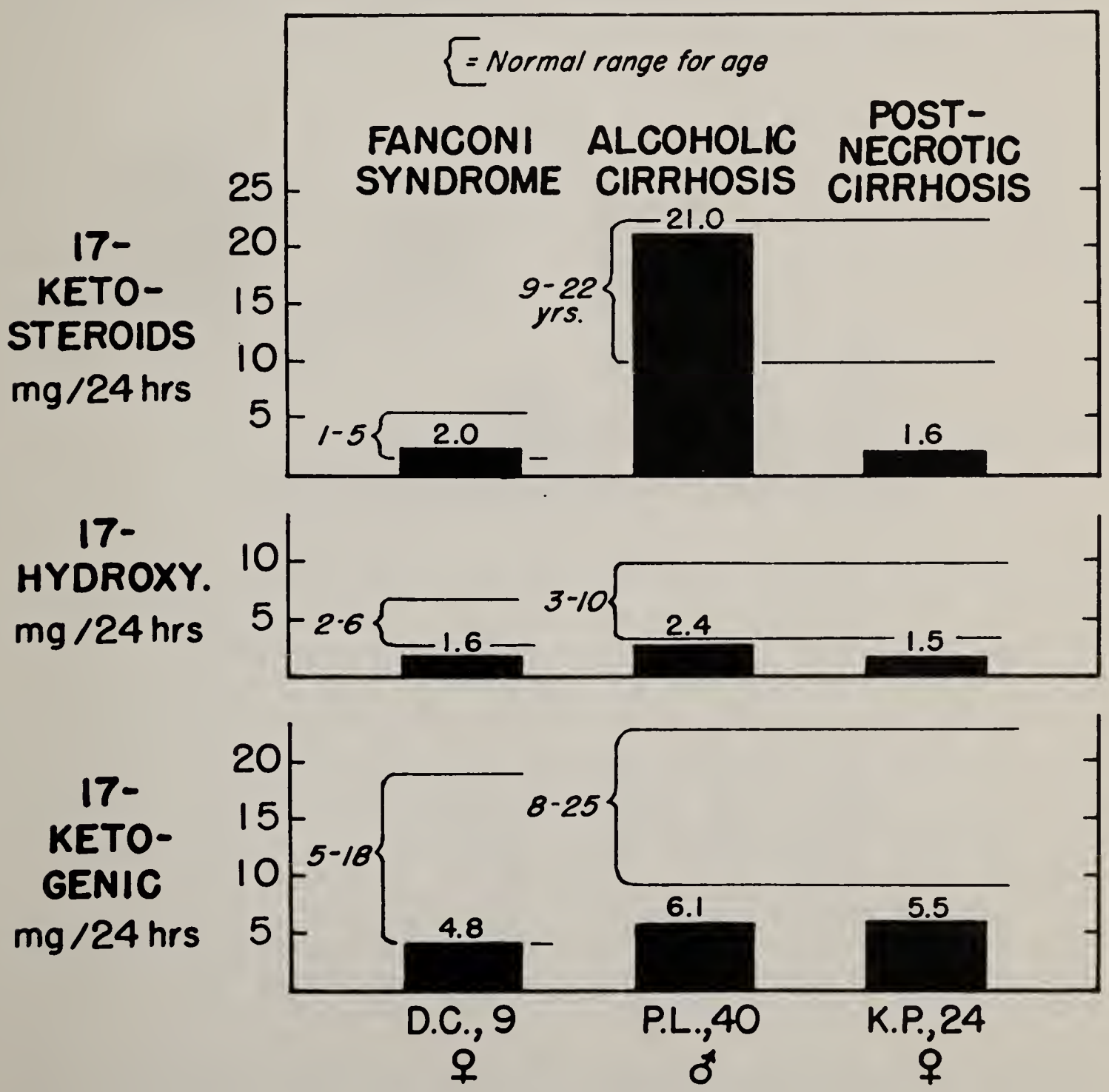

Fig. 5.—Patients with Liver Disease: 24-Hour Urinary Steroid Output.

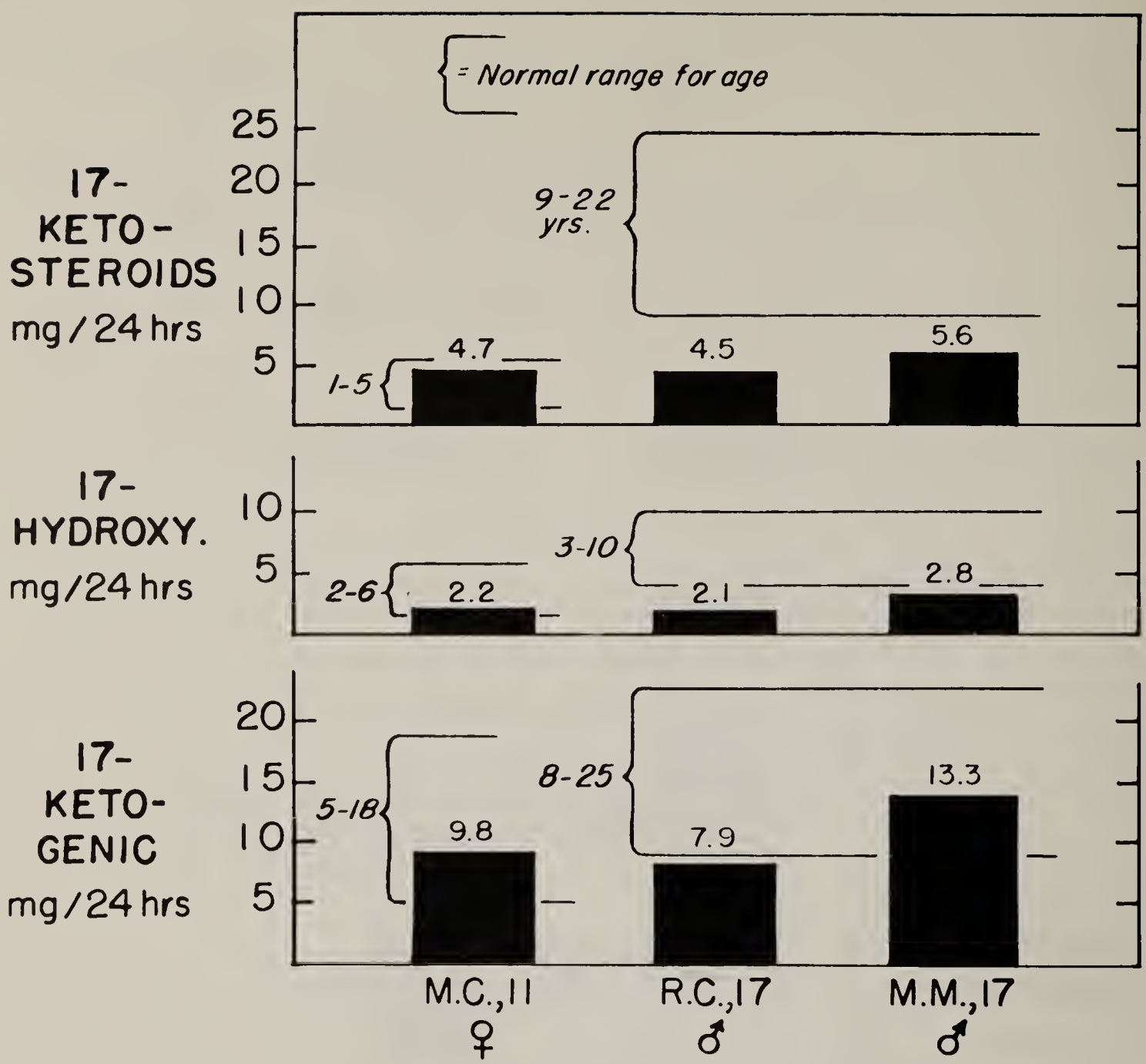

Fig. 6.—Siblings of Patients with HLD: 24-Hour Urinary Steroid Output.

recent reports in which children with HLD were similarly stimulated with ACTH and produced sharp curves consistent with the normal adrenal response.[18] The question raised at this point was whether the non-progression of the disease process in this HLD patient is not perhaps related to his relative adrenal insufficiency. Significantly, the 24-hour urines collected during and after ACTH stimulation still failed to produce abnormal chromatographic deposits.

Study No. 6: The final in this series of clinical studies was a prolonged dexamethasone suppression test undertaken on the same HLD patient that had been investigated initially (patient number 1, R.K.). It was felt that if the adrenal gland were truly implicated in this disease process (by producing an abnormal steroid that altered renal function and suppressed phagocytic activity) that adrenal inhibition should produce some indicative changes. Such a suppression would best be achieved with a drug that had no anti-inflammatory activity but would interrupt the pituitary-adrenal feedback mechanism to prevent adrenal steroid formation. As yet, there is no such ideal drug available for this test. It was decided to use dexamethasone, which might give some of the answers about renal function but, because of its own high anti-inflammatory activity, would pre-

vent investigation of the possible "pure" reticuloendothelial response to the suppression.

The experiment was performed over a period of seven weeks, during which time 0.5 mg. dexamethasone was given orally every six hours. During the period of suppression, weekly serum and 24-hour urine samples were collected and assayed for copper, calcium, uric acid and glucose. The patient developed, over this time, many additional typical Cushingoid signs, including moon facies, peripheral edema, and labile emotions.

In analyzing the results, particular attention was focused on the serum and urine copper. It was observed that the abnormally low control level of serum copper (32 microgrms.%) gradually rose to a normal concentration (112 microgrms.%) by the 25th day, then decreased (Figure 8). This finding is particularly interesting in light of the recent studies by a group that studied serum copper levels in children.[19] These workers found that, following long periods of steroid treatment, serum copper became depressed to the low level seen in HLD, without associated hypercupresis.

The serum calcium concentration, which normally decreases with steroid administration, showed a steady rise during the period of suppression, with a relative decrease in the urine at the 25th day (Figure 8).

Finally, a look at the serum glucose levels showed them to be in the normal fasting range thruout the entire course of the test period, but there was nonetheless a gradually increasing glycosuria

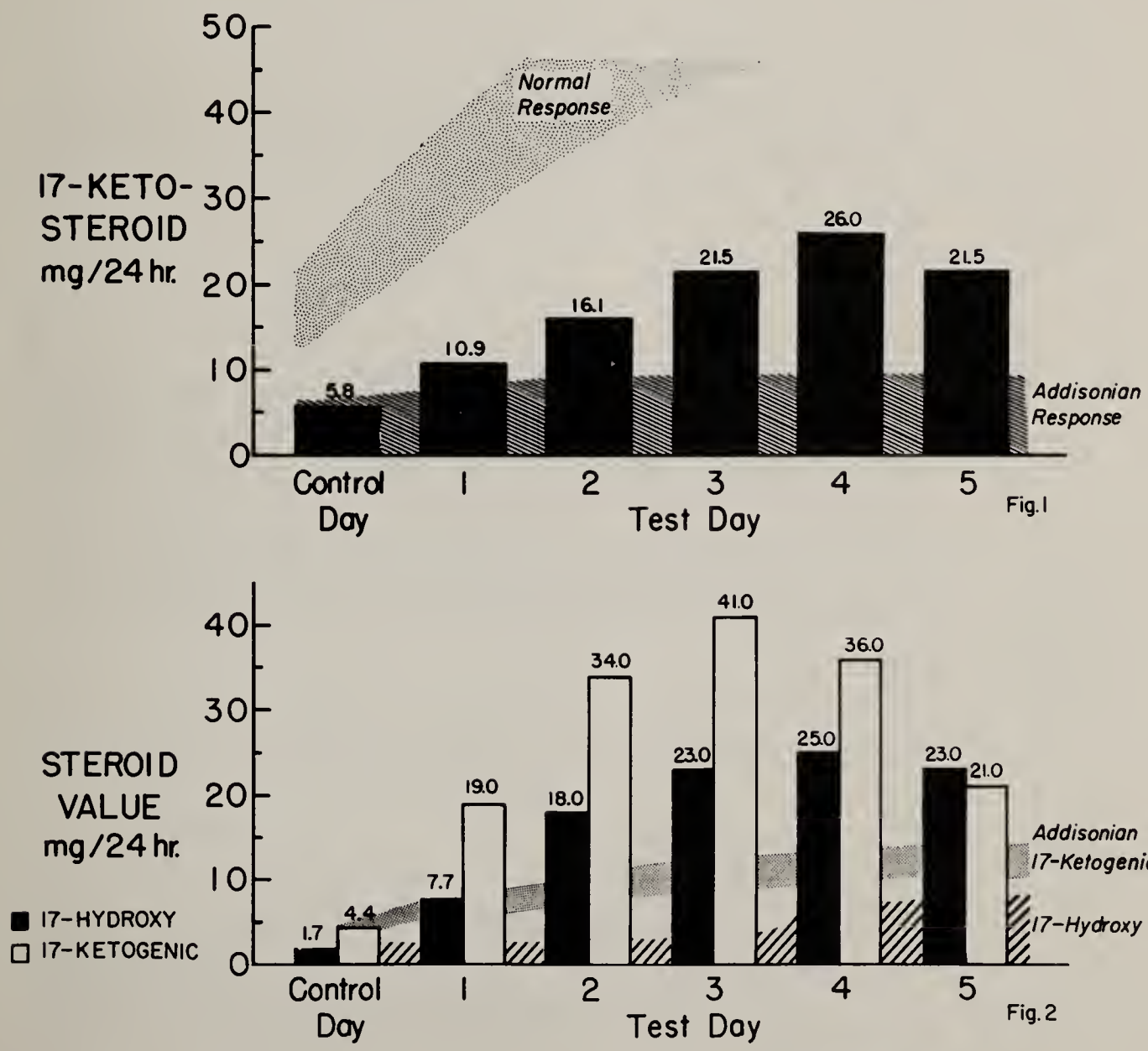

Fig. 7.—Quantitative Urinary Steroid Output with Stimulation by ACTH (Coricotropin Gel 80U I.M. Daily).

through the 25th day, with an abrupt absence of urinary glucose one week later (Figure 8).

Of further significance are the steroid chromatography results during adrenal suppression. After the first week of dexamethasone, the urine of this patient (who had formerly shown such a heavy abnormal steroid deposit) ceased to have any chromatographic evidence of abnormal steroid output.

Given this disappearance, it might be

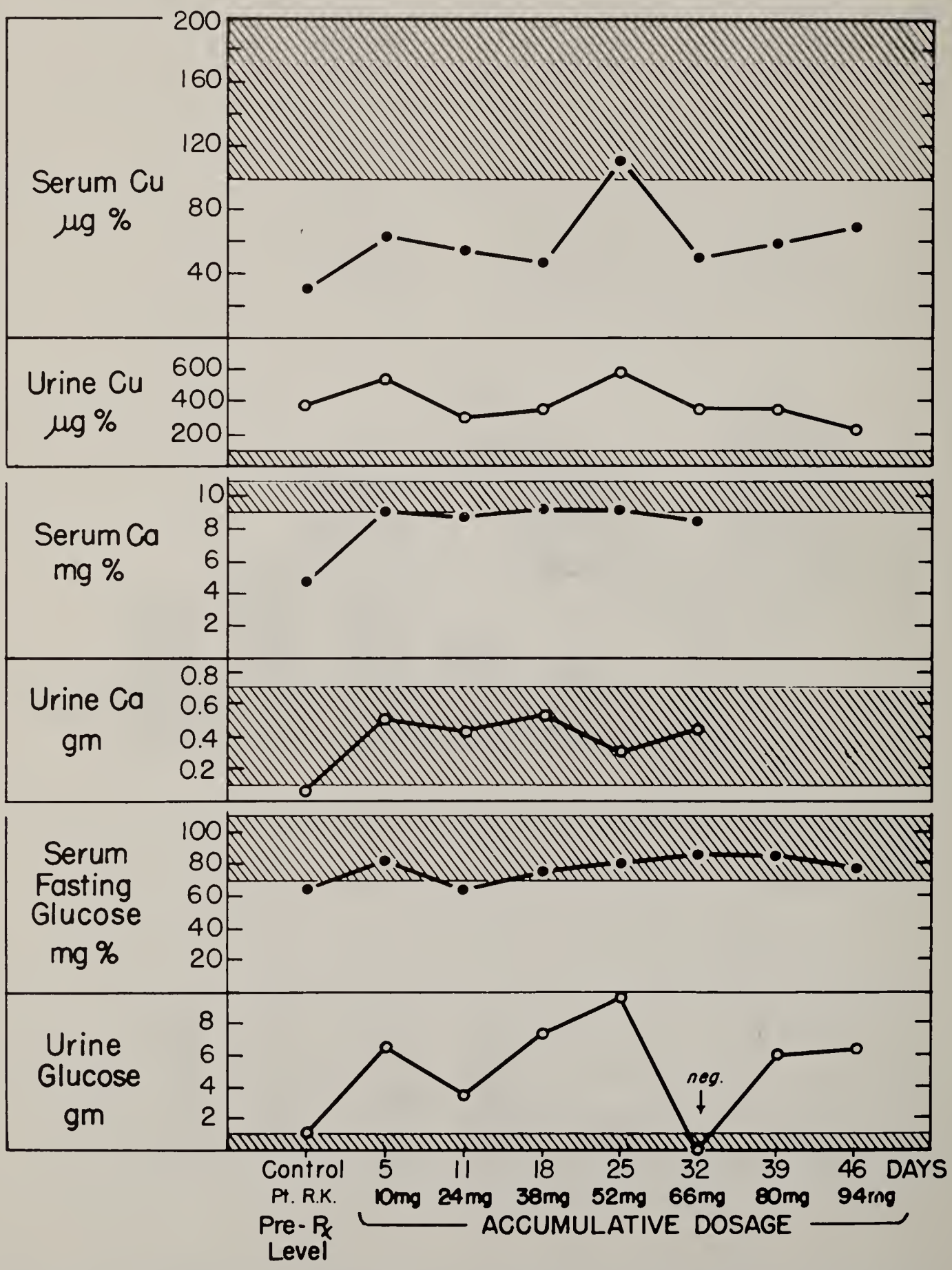

Fig. 8.—Adrenal Suppression with Dexamethasone in a Patient with Hepatolenticular Degeneration. Values of Serum and Urine Calcium not available after the 32nd day.

appropriate to think further about the results in this study. The serum copper and calcium, for example, initially rose during suppression. Only later in the course of the experiment did they become depressed (Figure 8), which is the normal response to dexamethasone. Eventual but definitely late decreases also occurred in the urinary copper, calcium, and glucose. One speculative explanation for these variations might lie in a kind of double role here for dexamethasone, because of the endogenous steroid situation in HLD, with its abnormal steroid at work. Early in the suppression, the overall effect of the dexamethasone is perhaps primarily due to its inhibitory action on the abnormal steroid, thus allowing a release phenomenon and subsequent return to normal of serum substances formerly held down by the endogenous steroid. Later, when abnormal steroid production has been totally suppressed by the dexamethasone, the expected (usual) dexamethasone effect appears on these serum and urine substances.

Intrinsic to these explanations is the assumption that the disappearance of the abnormal spot by chromatography is causally related to the serum and urinary changes.

SUMMARY

A new, more inclusive way of looking at the patho physiology in HLD has been discussed and investigated. It is proposed that the disease process is a function of inhibition of phagocytosis, perhaps caused by an abnormal steroid which also produces the abnormal renal function. In this conceptualization, copper is only indirectly involved and secondarily implicated. The presence of the abnormal steroid, bound to tissue proteins in liver, brain and muscle and exerting its potent chelating effect there (as described for steroids by Weisel[20]) could account for the increase in tissue copper in these areas. It could also help explain the low serum copper, which is a known steroid effect.

Although the material presented here is still unconfirmed and some of the interpretation perhaps premature, the evidence appears to be highly suggestive. Surely, most neurologists would agree that, to date, the status of understanding of this disease process has left much to be desired, when evaluated in terms of rationale and effectiveness of the best presently available therapy. The main line of defense against HLD, the various chelating agents, is essentially empirical treatment. It is recognized as "stop-gap" medicine and hardly designed to eliminate the basic defect. As has been pointed out, the fact that the effective chelating drugs appear to be those that stimulate phagocytosis, implies that more than copper chelation is at work here. Investigators interested in understanding HLD and those looking for more definitive treatment could thus perhaps profit from this new pathophysiologic orientation. If this hypothetical explanation of the disease is correct, it is conceivable that the future curative and preventive approach to HLD might be some form of adrenalectomy.

APPENDIX
Brief Case Descriptions of Patients with HLD

Patient No. 1: R. K. is a 36-year-old white male who, at age 19, developed a slight tremor of his right hand, slurred speech, and personality changes. He was subsequently discharged from the Navy with a diagnosis of "schizophrenia." After that he developed a severe tremor of all extremities, a pronounced dysarthria, broad-based gait, and Kayser-Fleischer rings but has had no jaundice, spider angiomata or palmar erythema. He has been hospitalized for the last 16

years as an ambulatory patient, during which time he has been treated with BAL, penicillamine, potassium sulfide, low copper diet. Signs consistent with adrenal hyperfunction are osteoporosis by X-ray, skin of fine texture with increased superficial vascularization (due to decreased collagen), glycosuria (but normal blood sugar levels), and a persistent lymphopenia.

Laboratory Data: Serum: copper 23 μgms%, ceruloplasmin 0.00 O.D. (normal 0.4 O.D.), calcium 4.6 mg%, uric acid 2.3 mg%, glucose 64 mg%. Liver Function: thymol turbidity 11, cephalin flocculation 3 plus, prothrombin time 40%. Urine (volume of 2200 cc. in 24 hr.): copper 380 mg/24h, calcium 0.3 gm/24h, uric acid 850 mg/24h, glucose 1.1 gm/24h.

Patient No. 2: R. W. is a 17-year-old white Jewish male who, three years ago, developed behavioral changes consistent with schizophrenia and at the same time developed slurred speech and some difficulty with coordination and posture. Since then, he has developed swallowing difficulty, tremor of his arms and hands, flexion contractures at the knees and hips, and dysarthria. Kayser-Fleischer rings are present, but there have been no physical signs of cirrhosis. He has been hospitalized for the past two years, during which time he has received treatment with BAL, penicillamine, potassium sulfide, and dietary control. His signs of possible adrenal hyperfunction are high blood pressure (200/90), skin with apparent superficial vascularization as in patient No. 1, and acne.

Laboratory Data: Serum: copper 42 μgm%, ceruloplasmin 0.04 O.D., calcium 10.1 mg%, uric acid 2.8 mg%, glucose 90 mg%. Liver Function: thymol turbidity 1.5, cephalin flocculation 1 plus. Urine (24-hr. volume of 1190 cc.): copper 500 mg/24h, calcium 103 mg/24h, uric acid 380 mg/24h, glucose (qualitative) negative, protein (qualitative) trace.

Patient No. 3: S. M. was a 21-year-old white female who developed her disease eight years ago and progressed to a stage of total helplessness. She had flexion contractures of all extremities, was dysarthric and comatose at the time of examination.

Laboratory Data: Serum: The patient expired before these studies were completed. Urine (565 cc./24h): copper 19.3 μgm/24h, calcium 79.0 mg/24h, uric acid 100 mg/24h, glucose 70 mg/24h.

Patient No. 4: M. G. is a 34-year-old Jewish female who, fifteen years ago, developed abdominal symptoms, scanning speech, personality changes, spasticity, and a progressive tremor. Since that time, she has developed severe contractures and dysarthria. Kayser-Fleischer rings are visible, but she has had no jaundice, palmar erythema or spider angiomata. During the couse of her disease she has been treated with BAL, versene, and penicillamine. Her signs of adrenal hyperfunction are osteoporosis, characteristic skin appearance, acne, amenorrhea, and glycosuria.

Laboratory Data. Serum: copper 22 μgm%, ceruloplasmin 0.150 O.D., uric acid 1.2 mg%. Liver Function: cephalin flocculation 4 plus. Urine (450 cc./24h): copper 102 g/24h, calcium 58 mg/24h, uric acid 296 mg/24h, glucose 1.12 gm/24h.

Patient No. 5: M. M. is the 17-year-old brother of the deceased S.M. He is presently asymptomatic. Kayser-Fleischer rings are his only abnormal physical sign. Also, he does have glucosuria and uricosuria, which may be signs of adrenal hyperfunction.

Laboratory Data. Serum: copper 32 μgm%, ceruloplasmin 0.2 O.D., calcium 10.7 mg%, uric acid 3.7 mg%, glucose 85 mg%. Liver Function: cephalin flocculation negative, thymol turbidity negative. Urine (1210 cc/24h): copper 213 μgm%/24h, calcium 0.4 gm/24h, uric acid 854 mg/24h.

Patient No. 6: I. S. is a 52-year-old white Jewish male who, twenty-three years ago, developed a slight tremor of his hands and personality changes. He was treated with psychotherapy but became steadily worse until 1954 when he developed "ulcers" and had an acute

hemorrhagic crisis which required a subtotal gastrectomy. Since that time he has been treated with BAL, penicillamine, and other chelators. He has slurred, halting speech, a broad-based gait, and an intention tremor but is at home, ambulatory and comfortable. Kayser-Fleischer rings are present, but there are no physical signs of liver disease. In contrast to the other patients with their variable signs suggestive of increased adrenal activity, this patient has the clinical findings, as discussed in the text, of adrenal insufficiency.

Laboratory Data. Serum: copper 32 μgm%, ceruloplasmin 0.02 O.D., calcium 10.1 mg%, uric acid 2.9 mg%, glucose 90 mg%. Liver Function: thymol turbidity 3.7, ceph. floc. 1 plus, A/G ratio 4.6/2.5. Urine (1300 cc/24h): copper 175 μgm/24h, calcium 81 mg/24, uric acid 545 mg/24h, glucose 3.3 gm/24h, protein (qualitative) trace.

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MASSIVE HEPATIC NECROSIS FOLLOWING HALOTHANE ANESTHESIA

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INTRODUCTION

Since Raventos[1] reported liver necrosis in animals following the administration of halothane anesthesia, cases have been described in man following the use of this anesthetic agent. More than ten deaths have been reported since it was introduced in 1956. An estimated twelve million halothane anesthetics have been given in the United States since its introduction.[2]

We are reporting a case of massive hepatic necrosis resulting in the death of a patient who received two halothane anesthetics, within a thirty-day period, for elective surgical procedures.

CASE HISTORY

First Admission: This 61-year-old white female was admitted to Presbyterian-St. Luke's Hospital, Chicago on 6/25/63 for skin grafting procedures to her left hand.

Approximately thirty years prior to admission the patient received radiation therapy to both hands for "dermatitis." She noted that the skin of her hands had slowly become thin and atrophic, and more recently there were ulcerations of the palmar surfaces of both hands. The patient had received 100,000 units of Vitamin A daily for the past two years because of alopecia areata. She had also been taking 2½ mg. of prednisolone daily for the past eight years for mild joint pains unrelieved by salicylates.

Physical examination revealed a well developed, well nourished white female in no acute distress. B.P. 116/74, Pulse 88/min., Temp. 98.8°F. The chest was clear. No palpable masses were noted in the abdomen, and the liver was not enlarged. The sclerae were clear. There was atrophy and ulcerations of the skin and subcutaneous tissue of both palms and the volar surfaces of the fingers.

Because the patient had been on steroids, she was given cortisone acetate 50 mg. intramuscularly on the evening prior to surgery and again on the morning of surgery. During the surgical procedure she received an intravenous infusion of 5% dextrose-in-water containing 100 mg. of sodium succinate ester of hydrocortisone. She was given meperidine hydrochloride 50 mg. and atropine sulfate 0.4 mg. intramuscularly preoperatively. Anesthesia consisted of intravenous infusion of thipental sodium and succinycholine. Halothane and nitrous oxide were given by inhalation. The surgical procedure consisted of partial amputation of the left index finger followed by a split-thickness skin graft to the left thumb. Total anesthesia time was two and one-half hours. The blood pressure remained stable throughout the procedure. Cortisone was given postoperatively in a tapered dose schedule. The patient had an uneventful post-

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operative course and was discharged on the fourth post-operative day. Final diagnosis was chronic radiation dermatitis and epidermoid carcinoma-in-situ from the skin of the left thumb.

Second Admission: The patient was readmitted on 7/21/63. She had no complaints and the physical findings were essentially unchanged from the previous admission. The patient received the same steroid regimen as on the first admission. Pre-operative medication consisted of meperidine hydrochloride 75 mg., promethazine 25 mg., and atropine sulfate 0.4 mg. Thiopental sodium, halothane, succinycholine and nitrous oxide were again used during the surgical procedure which consisted of skin grafting procedures to the digits of the right hand. Total anesthesia time was two and one-half hours and the blood pressure remained stable throughout the procedure.

On the evening of surgery, the temperature rose to 100°F. The next morning the temperature was 102°F. The patient had three syncopal attacks during the first post-operative day when she attempted to get out of bed. On the second post-operative day she complained of nausea, anorexia, and vague abdominal pains. The blood pressure fell to 80/66. The steroid dosage was increased. On the fourth post-operative day the patient developed dark urine with clinical evidence of jaundice. The liver became palpable two centimeters below the right costal margin and was tender. The spleen was not palpable and there was no evidence of ascites. Vitamin K was given and the cortisone dosage was tapered as quickly as possible. Parenteral fluids were begun on the fifth post-operative day when she became disoriented. Her condition continued to deteriorate and she expired on the fifteenth post-operative day. Post-mortem histopathological studies revealed massive centro-lobular necrosis of the liver with scattered islands of regenerating hepatocytes. The portal spaces showed proliferating biliary ductules and infiltrates of chronic inflammatory cells. (See figure 1.) The kidney findings were unremarkable.

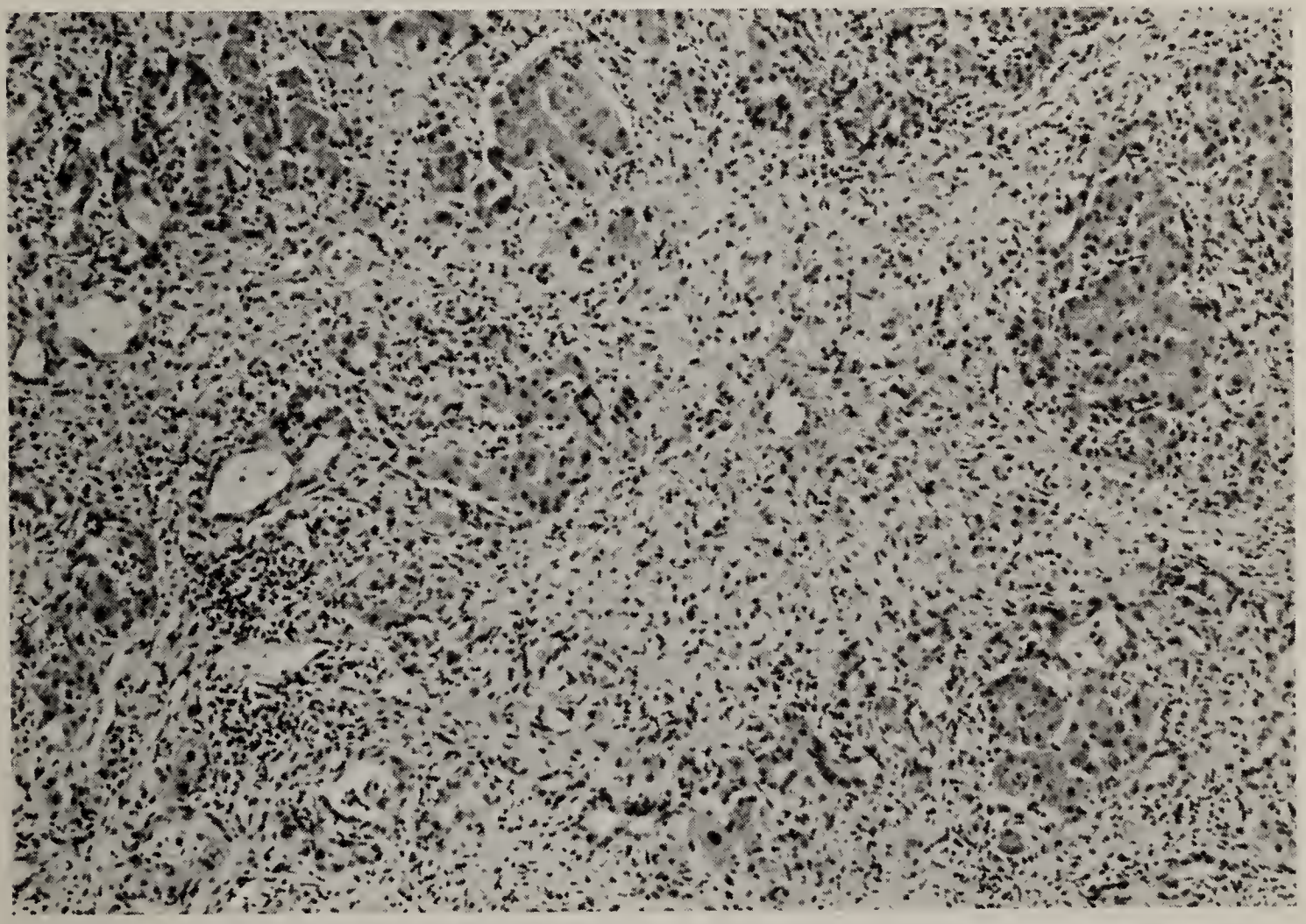

Fig. 1.—Photomicrograph of post-mortem biopsy of liver. Note the massive centro-lobular necrosis. The portal spaces show proliferating biliary ductules and infiltrates of chronic inflammatory cells.

DISCUSSION

Evidence is mounting that there is a casual relationship between halothane and liver damage. In 1956, Raventos[1] reported mild necrosis of the central portion of the liver lobule in animals following the prolonged administration of halothane. Virtue[3], in 1958, reported a case of a thirty-nine year old white female who died eleven days post-operatively following biliary tract surgery done under halothane anesthesia. Autopsy revealed severe central, midzonal, and peripheral necrosis without focal abscesses. Jones et al[4]. administered various anesthetic agents to 1500 white mice by esophageal instillation. Histologic studies done seventy-two hours later demonstrated fatty infiltration of the liver.

The patient described in this article tolerated the first procedure well and was discharged on the fourth day post-operatively. She did not receive blood or blood products. Our hospital uses disposable needles and there was no history of exposure to hepatitis. On the second hospital admission, the temperature was normal pre-operatively and

TABLE I—LABORATORY DATA

Lab. Test	6/25/63 1st Admission	7/21/63 2nd Admission	7/25/63 2nd Post-op Day	7/27/63 4th Post-op Day	7/29/63 6th Post-op Day	8/1/63 9th Post-op Day	8/2/63 10th Post-op Day	8/5/63 13th Post-op Day	8/7/63 15th Post-op Day
Hemoglobin gm%	13.6	13.0		14.9			12.1	10.1	
WBC/mm³	5,500	4,800			8,100		7,800		
Cephalin Flocculation							3+		
Thymol Turbidity				2.4	1.0		1.4		1.2
Alkaline Phosphatase				2.8	9.4		7.8		8.2
Serum Bil. Direct			0.9	7.6	9.3		17.3		18.8
Serum Bil. Total			2.8	13.6	15.6		27.6		31.4
SGOT				2,000	1,760		680		400
Serum ICD					3,940		930		460
Serum Na mEq/L			140		141	137			121
Serum CL mEq/L			102		105	102			81
Serum K mEq/L			4.3		3.9	4.7			5.7
Serum CO_2 mEq/L			27.8		27.8	27.3			25.2
BUN mg%	20				7.0				17
FBS mg%			72						
Serum Albumin gm%									2.7
Serum Globulin gm%									2.1

the WBC was not elevated. The liver was not palpable. The anesthesia record shows no evidence of hypotension. It would be difficult to judge the adequacy of ventilation during the procedure.

The massive necrosis was well demonstrated by the SGOT of 1760 units and the ICD of 3940 units on the sixth postoperative day. The finding of massive liver necrosis on histopathologic examination confirmed the clinical impression. (Details of laboratory studies in Table 1.) Although other drugs were used in this patient, none of them have been reported to produce the massive necrosis which was present in this patient.

It is of interest to note the recent report by Cohen[5] suggesting that butenes, forming in halothane stored in copper-lined vessels, are the hepatotoxins responsible for liver damage.

SUMMARY

We have presented a case of death due to massive liver necrosis which followed halothane anesthesia. The patient had no evidence of pre-existing liver disease and became clinically ill following the second of two halothane anesthetics given within thirty days.

Although other drugs were also used, it seems likely that there may have been a casual relationship existing between the administration of halothane and the patient's massive hepatic necrosis and subsequent death.

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THROMBOANGIITIS OBLITERANS:
A Juvenile or Presenile Form of Atherosclerosis Obliterans

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During the past 40 years since Buerger[1-4] reported the results of his clinical and pathologic studies and observations on presenile or juvenile gangrene, intensive investigations of the disease process have been rewarding. Excellent progress has been made in the early recognition and treatment of the disease. Prior to 1930, serious clinical symptoms such as gangrene and infection of the extremity were present before the disease was recognized; and by then treatment was entirely empirical and mostly valueless. The progress is due to new tests, procedures, and mechanical equipment, as well as experienced interpretation and knowledge[5,6] that were not available at the time of Buerger's pioneer investigations. The results of our active participation in studying the disease during all this time support the contention that the vascular disease in thromboangiitis obliterans is a presenile or juvenile form of atherosclerosis obliterans.

HISTORICAL BACKGROUND

Thromboangiitis obliterans was described originally by Van Winiwarter[7] in 1879, as endarteritis obliterans. Many names have been given to the disease. The fully descriptive term thromboangiitis obliterans was coined for the disease by Buerger[1]. He noted atheroma and thrombosis in the obstructive lesions as only "incidental findings." It is significant that with his vast clinical experience and pathologic studies of amputated extremities he reported only three autopsies; these had extreme atherosclerosis at ages 21, 24, and 35 years. He noted that "marked atherosclerosis" also occurred in young individuals without thromboangiitis obliterans. The limitation in the interpretations of his findings was due to the fact that early peripheral arterial atheromata are symptomless until luminal obstruction is sufficient to produce ischemia. Pathologic and experimental studies have shown that hemorrhage within an atheroma or rupture of an atheromatous

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plaque and thrombus formation account for the characteristic segmental occlusion[8-10]. Wartman[11], reported four autopsy specimens within one year with intraluminal obstruction in the leg arteries resulting from intimal rupture and thrombosis.

At the time of Buerger's publications, little was known about atherosclerosis; the process was generally considered to be a degenerative blood vessel disease. Anistschkow[12,13], a Russian, was the first (1913-1925) to produce experimentally in animals, atherosclerotic lesions by the feeding of fat and cholesterol. This provided a most important lead in understanding atherosclerosis. In 1933, Cowdry's[14] symposium on arteriosclerosis indicated the great interest and advances that had been made in the problem of arteriosclerosis. More recent symposia in 1954[15], and 1963[16], have contributed further to our knowledge of the disease. Many problems are now being investigated, especially the relation of cholesterol, fats and uric acid, urates and purine to arteriosclerosis. Clarkson and Newbergh[17], even in 1926, reported that proteins are as important as cholesterol in the arterial changes but this was not accepted by Anistschkow. Traut[18] (1954), reported specific arterial atheroma lesions in gout.

Leary[19] (1935), a dedicated public health official in Boston, reported the results of extensive experimental investigations on arteriosclerosis and obstructive arterial diseases. These were published in the Journal of the American Medical Association under the title of "Atherosclerosis obliterans the Primary Form of Arteriosclerosis: a metabolic disease." The significance of atherosclerosis and its role in producing intravascular thrombosis and obstruction was unknown prior to this time. Because of lack of funds, Leary was unable to study blood cholesterol levels that accompanied high cholesterol diets. Hass[20], and others[21], have reported the important reversibility of the experimental arterial lesions.

Since World War II, the advanced cases of thromboangiitis obliterans with unremitting pain and infected gangrenous toes and feet are rarely seen. Antibiotic and chemotherapeutic drugs have been effective in controlling infection due to sensitive organisms; however, the treatment of symbiotic resistant organisms is still discouraging.

Arteriograms of clinical and surgical specimens visualize frequently the multiple segmental character of the obstruction with normal intervening segments. Localized areas of peripheral arterial occlusion will produce minimum or absent subjective symptoms, especially in young individuals when adequate collateral circulation is present. Confluence, extension, or new areas of obstructive thrombosis will result in progressive circulatory deficiency and gangrene. The clinical course of the juvenile form of atherosclerosis obliterans is affected by the frequency of episodal and segmental main artery occlusion which stimulates greater development of the uninvolved collateral channels.

MATERIAL STUDIED

Since 1926, more than 6,000 patients have been examined with oscillometric readings, stabilized peripheral skin temperatures and response to vasodilatation, and many with arteriograms. Our first report on amputated extremities and arteriograms was made in 1928[22]. At that time, almost without exception, the progressive clinical arterial disease remained unrecognized until infection, uncontrollable pain, and gangrene of the foot or toes developed. The typical case, as seen before World War II, is illustrated in Figure I and Figure II. Antibiotics and most chemotherapeutic agents were unknown. The disease rarely involved more than one extremity at a time but recurrences involving another extremity were common.

The long-standing clinical course of many cases and the frequent inability to obtain relief from pain resulted in most patients seeking help from a succession of doctors; statistics from various institutions over a period of years included the

Mr. J. B., age 41
THROMBOANGIITIS OBLITERANS

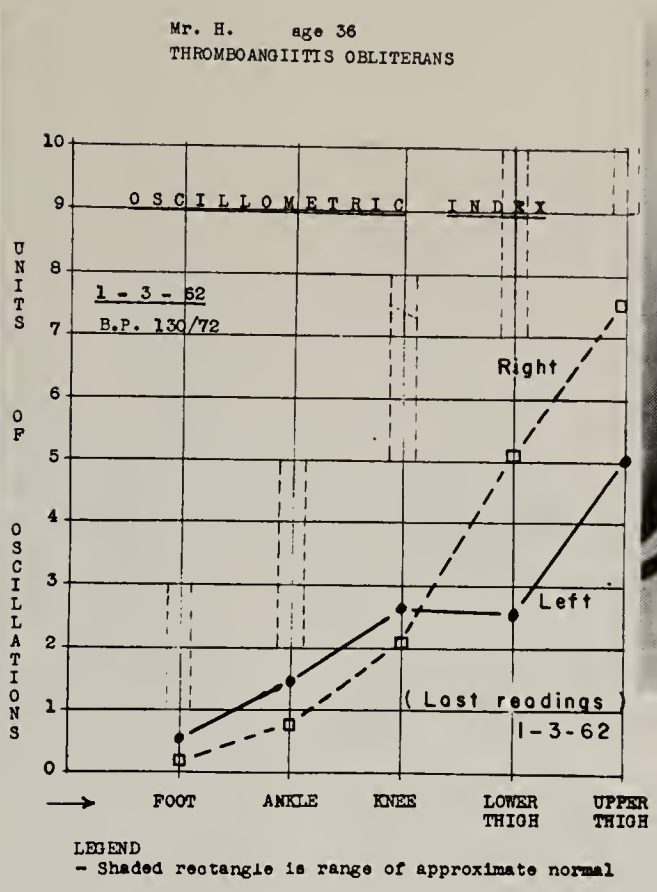
8-27-34	Oscillo. index (units)	
	ANKLE	THIGH
Right -	1.0	2.5
Left -	1.0	2.0

Fig. 1.—Progressive Course of thromboangiitis obliterans for more than 20 years. Gangrene and amputation of toes on both feet at age of 33 years (1928). Necrosis of tips of left second and third fingers occurred in 1929. Rapid healing followed intensive intravenous injections of inorganic sulfur and he returned to work as a barber. He never discontinued smoking cigarets. His last checkup was in April 1940 and in September 1941 he suffered a fatal coronary occlusion. Autopsy revealed complete occlusion of anterior coronary artery by a mass of clefts suggesting cholesterol crystals derived by embolism from an ulcerated atheroma. The aorta and peripheral arteries had extensive atherosclerosis, arteriosclerosis, and thrombosis.

same patients. However, at Rochester, Minnesota, with a local stationary population, there was a reported incidence of one case of thromboangiitis obliterans to 6,000 population[5]. After many years of disability, recurrences or recovery with minimum disability, deaths were almost always due to coronary thrombosis or to cerebral, renal, or mesenteric vascular thrombotic occlusion. Similar to Buerger's findings, four of our autopsies were deaths due to coronary occlusion in three cases and one case to renal artery obstruction ten years after aortic occlusion in a 19 year old female; extreme aortic and extensive peripheral artery disease was present[23]. The age of the patient at onset and the years of progress of the occlusive disease determines the type and severity of the pathologic vascular changes.

There have been no major amputations in our series of cases of thromboangiitis obliterans in the past 15 years. This is in marked contrast to Horton[24] of the Mayo Clinic, who found that 31 percent of patients had some type of amputation within the first three years, 39 percent within five years, and 59 percent within ten years of onset of the disease. Half of these were major amputations and half minor amputation; nine percent eventually required bilateral amputations.

4-26-37 (Initial readings) OSCILLO. INDEX		
	ANKLE	THIGH
RT.	0.4	3.0
LT.	1.5	3.0



SKIN TEMP. TOES (average °C)	RIGHT	LEFT
4-26-37 -	25.8	30.2
1-3-62 -	32.0	32.0

Fig. 2.—After refusing elsewhere a major amputation for gangrene of the right 3rd, 4th and 5th toes, and with severe constant pain in the foot, he was treated conservatively in our out-patient clinic (1936). He did not stop smoking until 1953. Local amputation of the gangrenous toes healed promptly and he resumed work as an automobile mechanic. Ten years later he returned, markedly overweight. The blood cholesterol varied from 167 to 341 mgs percent, depending upon his adherence to dietary restrictions. To date, no further circulatory trouble has occurred (June 1964).

DIAGNOSIS AND CLINICAL COURSE

The diagnosis of thromboangiitis obliterans is made because of the presence, in a young male, of circulatory obstruction in the extremities. This early stage is overlooked until disabling intermittent claudication and infection or gangrene develops in the toes or foot. Subsequent involvement of another extremity is observed frequently.

Biochemical blood studies may be important during certain stages of the disease. Almost every electrolite and metabolite have been investigated[5]. In our studies, many thousands of determinations have been made and analyzed[25]. During the acute active stage, without infection, the blood is very dark and viscid although special blood viscosity tests are not reliable or practical, the hematocrit reading and sedimentation rate are increased and the hemoglobin is either elevated or reduced. We found and reported reduced oxygen content of the arterial blood as low as 58 percent and this occasionally was accompanied by hemoglobin as high as 120 percent[25].

The metabolites have become increasingly important as our knowledge of the pathogenesis of atherosclerosis and arteriosclerosis increases. Almost all quiescent cases have recurrent periods of metabolic disturbances; abnormal lipid, cholesterol and carbohydrate metabolism, which may contribute to or are associated with the arterial disease. Purine metabolic disease is associated with severe atherosclerosis and arteriosclerosis[26]. Padora and Bendersley[27], reported evidence suggesting the relationship of uric acid metabolism with carbohydrate and lipid matabolism. A large percentage of our quiescent cases develop, over a period of years, hyperuricemia, hypercholesterolemia, or an abnormal hyperglycemia. The part that uric acid plays in the disease process is not clear. Unfortunately, uric acid is dissolved out

of histologic preparations by water and special alcohol preparations are required[28]. Within recent years, more importance has been attached to the frequent occurrence of elevated uric acid to 8, 10, or 12 mgs. percent, although 50 percent of patients with clinical gout and tophi have blood uric acid levels around 3 mgs. percent. Some authors describe atheromata as tophi.

Migrating superficial or deep thrombophlebitis may occur in thromboangiitis obliterans. The histologic picture in both the veins and arteries are almost identical, having atheromata formation, fibrosis of the organized and canalized thrombus, cholesterol deposits, giant cells or inflammatory cells.

Smoking may affect the blood in the acute phase of the vascular disease and may account for the dark color of the blood, increased viscosity, and cholesterol content under 200 mgs. percent[29]. With clinical recovery, the blood changes return to normal. These changes are similar to the physiologic effects of high altitudes. The oxygen content of the arterial blood is reduced with heavy smoking unless the blood pressure is elevated, respirations and pulse rate increased, and there is peripheral vasoconstriction[30,31]. Actually, smoking is an important factor in thromboangiitis obliterans but none of our patients ever discontinued the habit permanently.

Oscillometric studies are safe and reliable for accurately localizing the site, extent, and completeness of peripheral arterial obstructions. Stabilized peripheral skin temperature readings and the response to vasodilator tests will establish the patency and adequacy of collateral circulatory channels. In older individuals, the reserve collateral channels have become progressively involved by the vascular disease.

Visualization of patent vascular channels can be obtained by arteriograms but the risk and danger of (1) the injection producing further obstructing thrombosis; (2) the occasional serious allergic reaction to the radiopaque material, such as exfoliating dermatitis; and (3) vasospasm simulating organic arterial obstruction, does not justify their routine use. For peripheral vascular studies, 75 percent of the arteriograms are unnecessary; stabilized oscillometric and skin temperature readings give more reliable information as to the patency of the peripheral vascular channels than do the arteriograms. The important information on the distal collateral channels in the toes and feet are not obtained by ateriograms but are readily obtained by skin temperature studies. (Fig. III).

TREATMENT

Thromboangiitis obliterans, the juvenile form of atherosclerosis obliterans, is essentially a metabolic disease producing a complex process of peripheral arterial occlusion. Accordingly, treatment is directed to (1) the local infection in the toes and feet; (2) the peripheral ischemia caused by the arterial occlusion and vasoconstriction; and (3) the metabolic disturbances, such as hypothyroidism, hypercholesterolemia, hyperglycemia, and probably hyperuricemia.

Infection of the toes and feet should be given immediate attention and care. Routine wound cultures and sensitivity tests for antibiotic and chemotherapeutic drugs are obtained. Empirical broad-spectrum antibiotics are given while awaiting results of bacteriology tests; selective therapy is then given. Pseudomonas, B. proteus, and the aerobacter aerogenes organisms are the most resistant and unsuccessful to treat.

The vasoconstrictive ischemia can be ameliorated by vasodilator procedures. Vasodilator tests will establish the degree of organic and spastic ischemia. Vasodilatation is produced reflexly by low-heat electric pad placed on the abdomen and improvement in the organic ischemia is hastened by conservative negative and positive pressure treatment[32,33,34] to the extremity, or by lumbar sympathectomy[35]. Direct arterial surgery is not warranted or necessary in early limited segmental arterial occlusions. Patency of the vessel may occur spontaneously. Late extensive arterial occlusions of the periph-

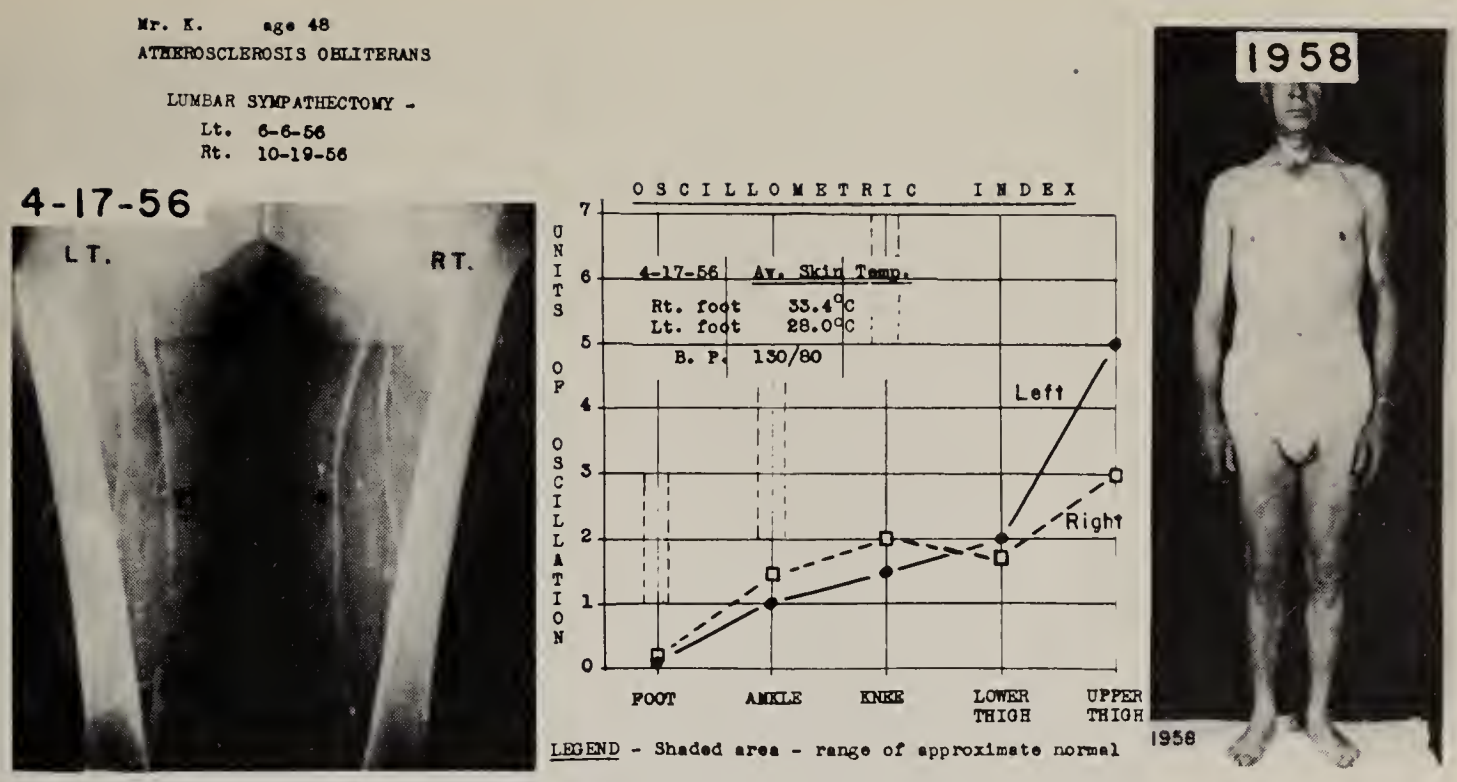


Fig. 3.—Progressive bilateral intermittent claudication of calf muscles limited walking slowly to two blocks (1956). Advanced main artery occlusion was confirmed by oscillometric readings and by arteriograms. Normal response of peripheral skin temperatures indicated good collateral circulation for lumbar sympathectomy to be most effective. The blood cholesterol of 502 mgs percent dropped to 305 mgs percent while patient continued on a low caloric and low fat diet. He was last seen in November, 1958. Recent inquiries revealed that he suffered a second coronary occlusion and is now convalescing (June, 1964).

eral smaller and larger arteries are not amenable to direct surgical procedures.

Metabolic disturbances contribute to all stages of the vascular disease. Our studies show that low oxygenation of the arterial and venous blood and low basal metabolism rates are elevated to normal levels by intravenous injections of inorganic sulfur and by thyroid therapy[30, 36, 37, 39]. In early thromboangiitis obliterans the blood cholesterol is not elevated and this may be related to the low oxygenation of the blood and atheroma formation. Routine treatment with inorganic sulfur compounds has been eminently successful. Thyroid medication is indicated even when the metabolism and thyroid isotope tests are normal. Dietary management includes restricted fat, cholesterol and caloric intake and control of the carbohydrate and purine diet. Over a period of many years, with many patients, this has not been a difficult or serious problem to control.

DISCUSSION

Many investigators have contributed to our present understanding of atherosclerosis as the primary lesion in thromboangiitis obliterans. Atheromata begin in childhood or even infancy and any artery in the body may be affected; the lesion may be resorbed, coelesce, or enlarged. Intramural hemorrhage will produce intraluminal enlargement of the atheroma, or intraluminal rupture of the atheroma with thrombosis may occlude the vessel (Fig. IV). The incidence of hemorrhage in relation to thrombosis is reported to be as high as 90 percent when close interval serial sections are made. This process produces, even in the healthy young, spontaneous strokes due to cerebral artery occlusion[40]; coronary, renal, and mesenteric artery occlusion occur also[41].

When the atheromatous plaque is present in the extremities, the secondary thrombosis may be small and limited

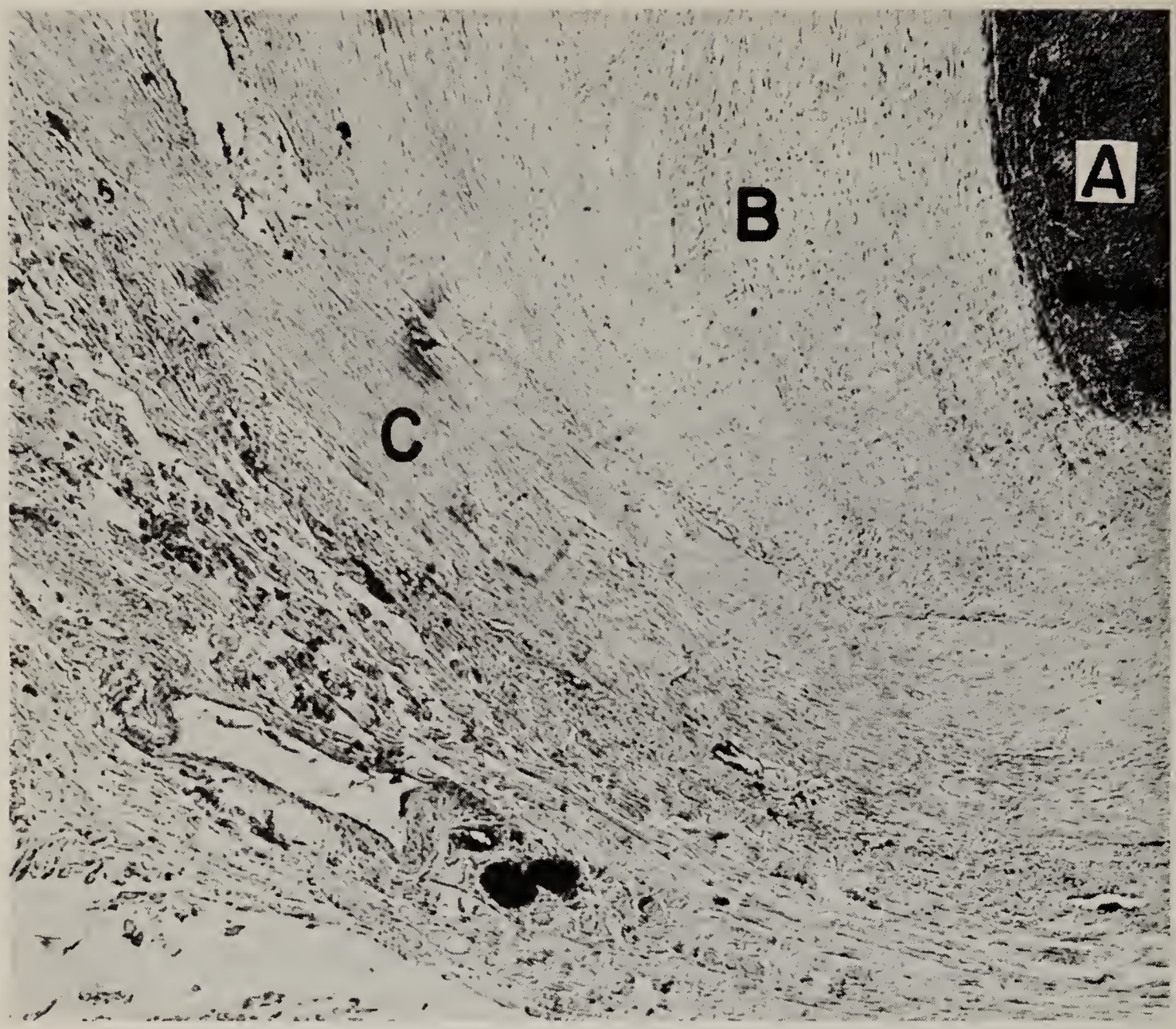


Fig. 4.—Photomicrograph—Thrombosis and severe atherosclerosis of the popliteal artery from surgical specimen of 34 year old male with thromboangiitis obliterans. Propagating occluding thrombus (A) originated at site of ruptured atheroma at another level; (B) subintimal atheroma; (C) media.

and will not seriously obstruct the circulation. Collateral circulatory channels are still uninvolved and adequate. As the obstructive process progresses the peripheral ischemia will increase. Cigaret smoking is not a causative factor for the arterial obstruction but the vasoconstriction resulting from smoking will further increase the ischemia.

Infection of the toes or fingers usually follows trauma with necrosis of the ischemic tissues. Symbiosis of infective anaerobic and aerobic organisms is frequently unresponsive to present therapy. The lymphatics from the infected gangrenous areas are carried along the vessels and may be responsible for some of the histologic inflammatory findings in the arteries and veins.

Thrombophlebitis of the superficial or deep veins of the extremity have identical lesions to those occurring in the arteries. Atheroma occur in the veins. Winternitz, demonstrated capillary communications between vein and artery that account for the "frequency of simultaneous arterial and venous involvement in thromboangiitis obliterans."

The presence of normal blood cholesterol in the young with atherosclerotic disease is an unexplained differential point with hypercholesterolemia in the

arteriosclerotic older patients. In long-term observations following recovery from the acute stage, the patients frequently will show evidence of diabetes, hypercholesterolemia, or hyperuricemia. This may be the long-standing terminal sequence of progression and regression in the course of development of the peripheral arteriosclerosis obliterans in older patients.

The typical histology of the vascular lesions in thromboangiitis obliterans represents the final dense fibrous tissue reparative process, the obstructing thrombus, cholesterol deposits with foreign body giant cell reaction, and/or the canalized thrombus. Hyperuricemia or gout is associated with extreme degrees of atherosclerosis and arteriosclerosis. Urates being soluble in the ordinary fixing solution precludes the usual tests for identifying them chemically or morphologically in the arterial lesions. However, they have been found in atheromatous deposits in the arteries as well as the heart valves.

SUMMARY AND CONCLUSIONS

Atherosclerosis with intramural hemorrhage or intraluminal thrombosis is the primary pathologic vascular condition responsible for the peripheral ischemia in thromboangiitis obliterans. Early limited arterial occlusion with adequate collateral channels precludes serious circulatory deficiency.

Cigaret smoking is not the primary cause of the arterial or venous occlusion but the vasoconstriction resulting from the smoking increases the peripheral ischemia.

Blood changes, in young individuals, may contribute to (1) the generalized atherosclerotic process, even in the absence of hypercholesterolemia; (2) the hemorrhage, rupture, and thrombosis of the plaque; and (3) the unusual reparative process in the vascular lesions.

Our present treatment which we have followed is highly successful in ameliorating the symptoms of the circulatory deficiency and improving the long-term prognosis of the disease.

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TRAUMATIC ANEURYSM OF THE THORACIC AORTA

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Traumatic thoracic aortic aneurysm of long-standing duration can be suspected on routine roentgenographic examination because of characteristic findings. This diagnosis can usually be confirmed by historical facts, combined with exclusion of other causes of thoracic aneurysm by appropriate clinical and laboratory procedures.

Rupture of the thoracic aorta due to blunt, nonpenetrating trauma occurs most commonly just beyond the origin of the left subclavian artery[1], and it seems likely that this location is preferred because of anatomic sites of fixation and differences in rates of deceleration. The aortic arch is most rigidly fixed by the great vessels and the ligamentum arteriosum, and during sudden linear deceleration of the thorax, this portion of the aorta decelerates at the same rate as the body as a whole, while the less rigidly bound central descending aorta is snapped forward by the decelerating force. These differences in rates of deceleration constitute a shearing or tearing stress which is concentrated at the point of maximum fixation[2] (Fig. 1).

Laceration of the healthy aorta as a result of indirect violence usually is complete and involves all layers[1], in which instance fatal hemorrhage most often occurs. Cases have been reported[3], however, in which such a catastrophe has been accompanied by patient survival of varying lengths of time, from hours to days. Most of these cases are characterized radiographically by widening of the mediastinum with obscuration of the aortic knob by para-aortic soft tissue density and fluid in the left hemithorax, findings which may lead to early recognition and successful treatment of acute aortic tear. It is reported[4] that 80% of those patients with traumatic rupture of the aorta will expire before reaching the hospital, and also that 80% of the survivors will die of secondary hemorrhage within three weeks of their injury.

Of particular interest here are those patients who incur trauma to the chest, and in whom an aneurysm is detected subsequently, often years later. Although traumatic interruption of the aortic wall usually involves all layers, the media and adventitia, or the adventitia alone, may be spared. These patients, then, may survive the acute injury and eventually develop an aneurysm as a result of hematoma formation and some element of dissection. Although aneurysm of the aorta due to chest trauma has been reported without apparent injury to the thoracic cage[5], most such patients suffer fractures of the ribs or sternum and often pneumothorax. Concomitant severe trauma of the head, abdomen, or extremities may draw attention away from the thorax, however, so that the initial findings of the aortic rupture may be overlooked.

Cases have been observed in which the sequence of events following a traumatic episode leads to reasonable assumption of the evolution of the radiologic findings of those aneurysms which are discovered years later[6]. In the acute phase, there is

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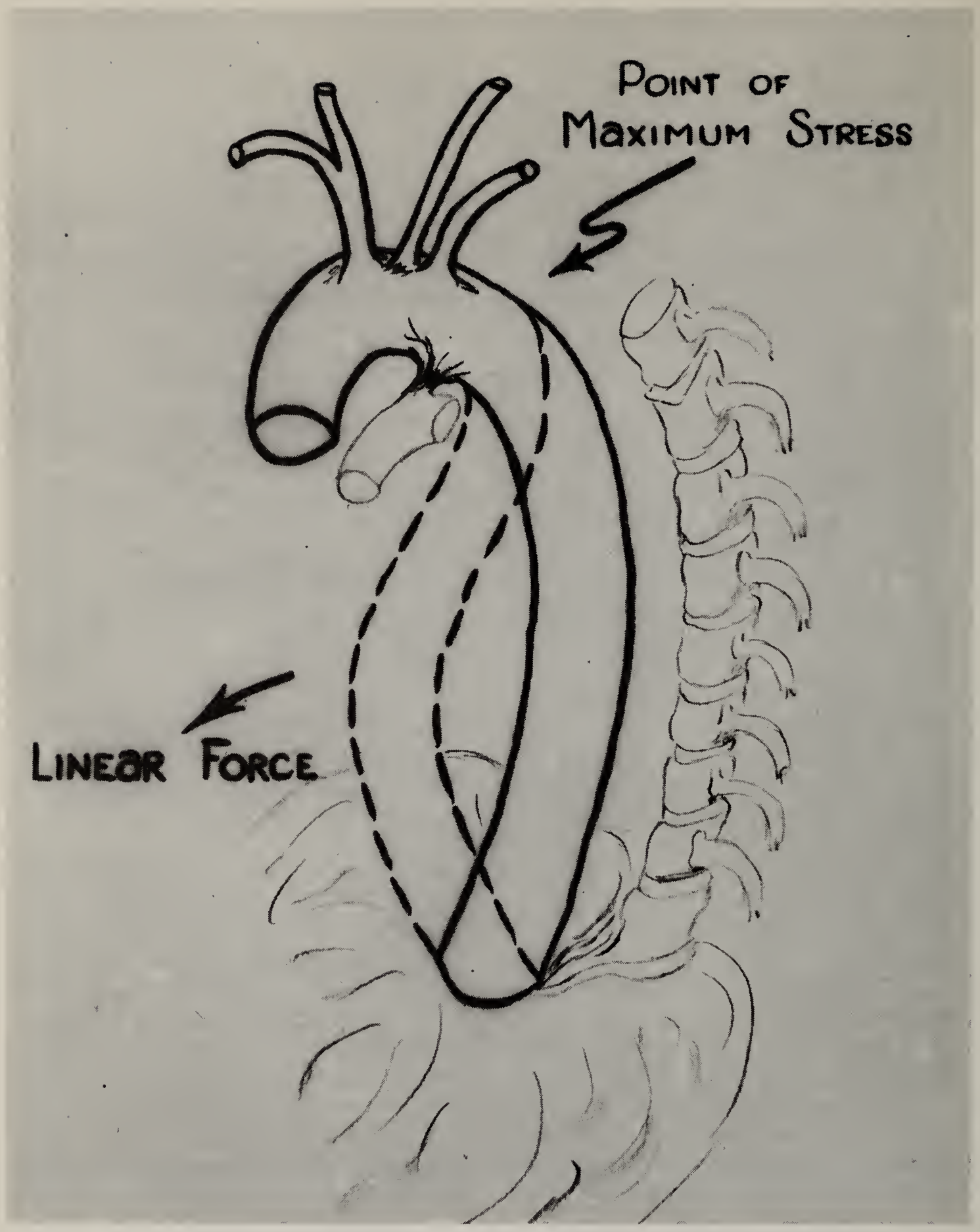

Fig. 1.—Mechanism of rupture of the thoracic aorta due to blunt, nonpenetrating trauma.

evidence of mediastinal hematoma. In a few days to a few weeks, a vague bulge appears adjacent to and indistinguishable from the aortic knob. Later, the aneurysm becomes localized and distinct, and, eventually, probably after a year, calcium is evident in its periphery, usually rather delicately deposited. The calcium which is present may result from an accelerated degenerative process in the damaged aorta or may occur entirely within the hematoma. Pathologic examination of surgical material from this group of chronic aneurysms usually shows arteriosclerotic changes with calcium deposition in the affected aorta.

Similar to other types of thoracic aortic aneurysms in this location, traumatic aneurysms may displace the barium filled esophagus, may or may not demonstrate pulsations during fluoroscopy, and may be opacified during angiography. The symptoms are likewise those of aneurysm in general, and it is noted that most cases of chronic traumatic aneurysm disclosed during routine x-ray examination are asymptomatic.

Differential diagnosis[7] of long-standing traumatic aneurysms includes predominantly syphilis and arteriosclerosis. Those of congenital origin are often associated with other malformations, such as coarctation, and degenerative diseases of younger patients are usually accompanied by changes elsewhere in the thoracic aorta and brachiocephalic vessels. Infectious destruction of the aortic wall, either as a result of bacterial endocarditis or contiguous erosion, is clinically apparent.

Fig. 2A is the frontal and Fig. 2B the lateral chest roentgenogram of a 36 year old male who was involved in an automobile accident fourteen years prior to admission. With the accident he sustained multiple fractured ribs, a lower extremity injury which required eventual amputation, and head trauma with unconsciousness for three days. A chest film taken one year later was reported to him as unremarkable. A routine chest roentgenogram examination recently led to the discovery of the aneurysm. Note the typical location of the aneurysm and the fine rim of calcium. Fig. 3 is a frontal frame from the thoracic aortogram. The

Fig. 2A.—Frontal roentgenogram of patient with a traumatic aortic aneurysm. Note typical location and fine peripheral calcification.

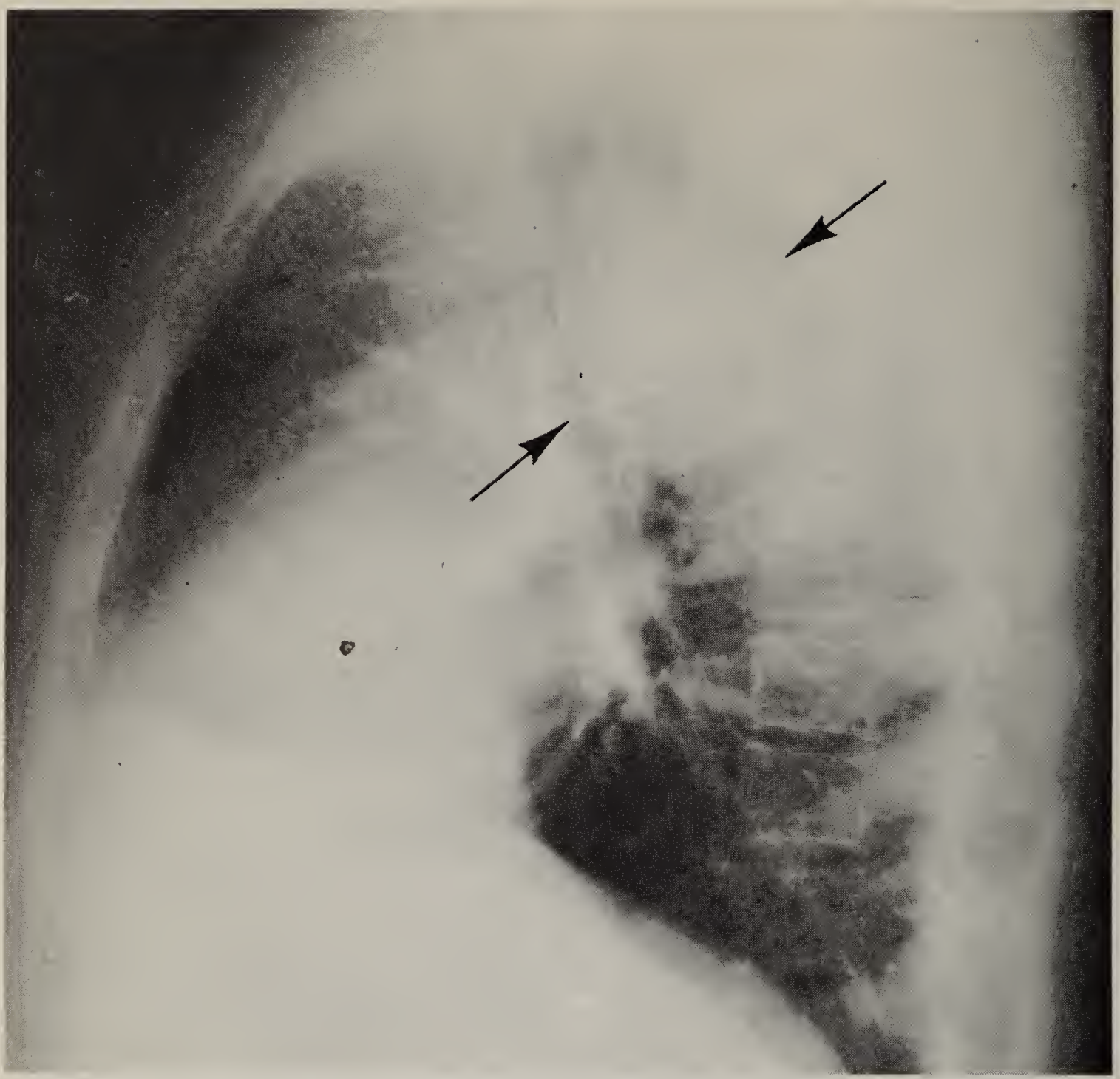

Fig. 2B.—Lateral roentgenogram of patient with traumatic aneurysm of thoracic aorta aneurysm outlined by arrows.

aneurysm is contrast-filled and originates beyond the origin of the left subclavian artery. The thoracic aorta and arch vessels are otherwise normal. The gross pathologic diagnosis of the surgical specimen was that of aortic aneurysm, and the microscopic study showed atherosclerosis with calcification.

SUMMARY

Traumatic aneurysm of the thoracic aorta can be suspected from routine chest films if the patient is in the younger age group and the aneurysm is located at the characteristic site just beyond the aortic arch and has a fine, peripheral rim of calcification. This diagnostic suspicion is strengthened by findings of old chest injury on the films, and it is confirmed by the history, physical examination, and laboratory procedures which exclude other possible causes for aneurysm here.

Fig. 3.—Thoracic aortogram in same case as Fig. 2. The aneurysm is opacified, and other vascular structures are normal.

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REVIEW ARTICLE

HYDROCOELE OF THE TUNICA VAGINALIS: A Historical Survey

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"*Conscientious and careful physicians allocate causes of disease to natural laws while the ablest men of science go back to medicine for their first principles.*"

Aristotle.

Although no disease can be considered insignificant, hydrocele of the tunica vaginalis may be categorised as a most benign disease except when it occurs as a sequel to disease of the testis. It is to the idiopathic hydrocele this paper is directed. Stimulated by the words of John Hunter—"Although the theory of the cure of hydrocele is very simple, yet no disease affecting the human body and requiring an operation for its cure, has called forth the opinions and pens of surgeons, so much as this disease."—I thought it of interest to study the evolution of the theories on both the aetiology and treatment of this condition up to the beginning of this century.

Of necessity, much of what has been written on this subject will have to be omitted, for in the words of Virchow, that, "Brevity in writing is the best insurance for its perusal," I will try to outline the important landmarks in the history of this condition.

The writings of Galen (130-200 A.D.), describe the surgical treatment of hydrocele of the tunica vaginalis. Although the radical treatment by surgical excision was recognised at this time, Galen advocated the cure of this malady by the use of a seton. "Through the tunica, a straight needle, reddened in the fire loaded with a thread of hogs bristle, was left in for forty days. After which the belly was covered with oil of roses and white of egg."

Five hundred years later the Greek physician Paulus Agineta proposed the following aetiology—"Blood brought to weak parts to nourish is converted to an inert watery substance." He describes vividly an operation performed at this time which although crude in its setting, resembles the present radical operation. "We operate in the above manner. Having shaven the pubes and scrotum, unless the patient be a boy, we lie him in the supine position on a bench and

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apply to his buttocks a cloth several times folded, and to the scrotum a sponge of considerable magnitude, and sitting on the left side of the patient we give directions to an assistant sitting on his right side, to draw the genital organs to the other side, and draw up the skin of the scrotum to the abdomen. We divide the scrotum longitudinally from the middle to near the pubes, the incision straight and parallel to the raphe which divides the scrotum in two parts, this incision is extended down to the tunica vaginalis . . . we lay bare the tunica vaginalis and divide it through the middle with a lancet for bleeding and having discharged into some vessel the whole or most of the fluid, we cut away the vaginalis. The wound was drained and remains open packed with wool dipped in oil." Later in the same text he describes access to the interior of the scrotum by the use of the cautery.

In 865 A.D. Rhases the Persian physician, though better known as the first to use animal gut as suture material, expressed the opinion that the only appropriate treatment for this condition was by simple puncture of the scrotum.

Abulcasis, (965 A.D.) an Arabian surgeon practicing in Cordova, realized that tapping of the fluid was not a curative procedure. In the French translation of The Surgery of Abulcasis, by Lucien Le Clerc, there is a description of hydrocele fluid as follows: "Ce liquide est devisement coloré', tantôt il est jaunatre tantôt trouble et noiratre, tantôt d'un rouge sanguin, tantôt blanchatre et c'est le cas le plus fréquent." From this description he could have been describing fluid from hydrocele, hematocele, spermatocele or a cyst of the epididymis. He noticed that people subject to hydrocele had a deposit laid down on the testis but drew no conclusions from this finding.

There is little to be found on this subject in English literature between these ancient writings and the Renaissance. In this era of our history a fusion of interest matured between those who artistically studied the nude body and those determined to make a more scientific study of its inner workings. The study of anatomy at this time was becoming recognized, and in England, Henry VIII passed a law in 1540, authorising the Barbers and Surgeons to use four bodies of executed criminals for dissection each year.

Three years later the Fabrica was completed by Andreas Vesalius. He described the tunica vaginalis in its normal state to be covered with a "kind of aqueous humour". Ambrose Paré' (Fig. 1) the famous French Surgeon was reputed to have coined the term 'hydrocele'.

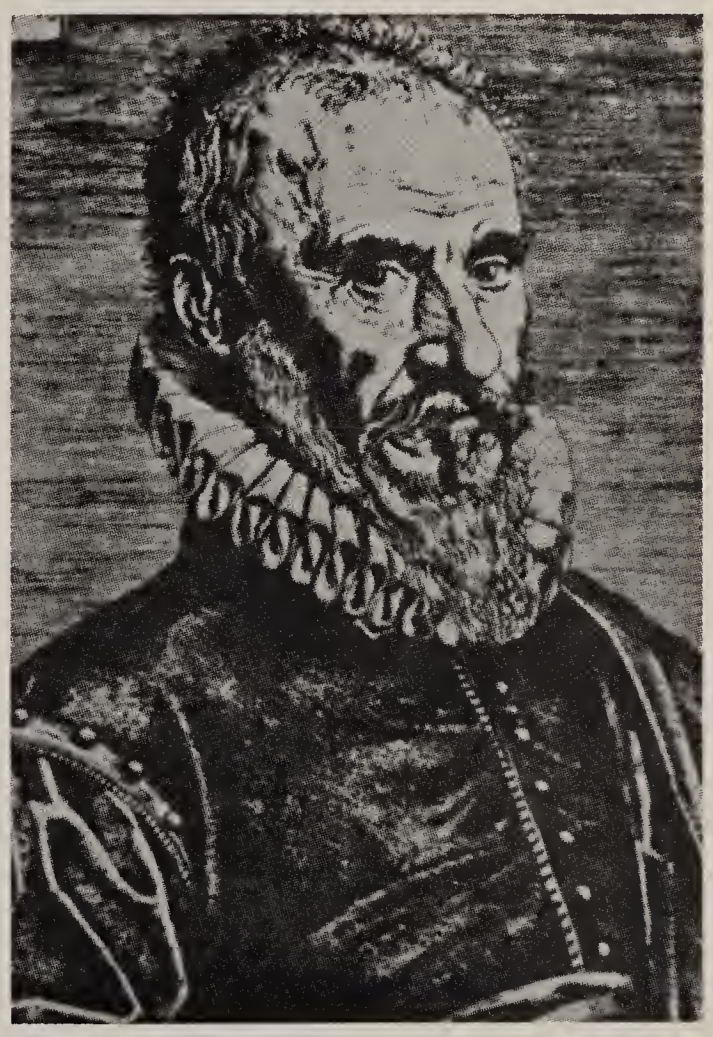

Fig. 1.—Ambrose Pare 1510-1580. By kind permission of Livingston Limited Publishers, Edinburgh, Scotland.

A century later, Valsalva and Malpighi* also recognised the presence of fluid within the tunica vaginalis and thought its purpose was to prevent coalition between the tunica vaginalis and the testis. Giovanni Morgagni (1682-1771), a pupil of Valsalva, is

*Letter XLIII, Article 16 et. seq. Morgagni

reputed to have been the first to consider that organs were the primary seat of disease. His conception of hydrocele was based on his observations on a number of bodies he dissected with this condition. He stated—"When I reflect upon all my observations with attention, I find none which does not show that those hydroceles of the tunica vaginalis which I have examined had derived their origin from the hydatids being ruptured there."

The advent of the 18th century brought with it a wealth of medical literature and much was written about this disease. The bulk of the effort was to find a radical cure without resorting to operation. Garrison describes this 'periwigged period' as being conceded the golden age. He describes the attire of the fashionable physician of this period —"He wore a powdered wig, a handsome coat of red satin or brocade, short breeches, stockings and buckled shoes, a three cornered hat, and bore a gold headed cane." In this period of history, therapeutic measures were mainly based on the traditional lines of bleeding, purging and diet.

In a treatise on this subject, Daniel Turner (1722), made a clear differentiation between hydrops testis and hydrops scrotalis or scrotal edema. Heretofore there had been some confusion on this particular point. He also stressed the need to differentiate between scrotal hernia and hydrocele and described transillumination of the scrotum as, "the use of a candle in a darkened room, showing transparency." He found that by heating hydrocele fluid in the flame of a candle it became gelatinous. His conclusions were that the fluid must be nutritious. He proposed a theory for the aetiology of this disease: "This malady now before us seems rather owing to a breach of some lymphatic or to a serious humour effused by the arteries of the investing membrane of the testis." For treatment he used the trocar for paracentesis, but at times applied caustic to the surface of the scrotum; the latter often led to indolent ulcers or incurable fistulae. It is of interest to record the management of a case of hydrocele, as described by Turner. "The case presented with an oblong tumour hanging on one side of the scrotum, like the testis of a bull, but much larger, stretched out from the bottom and growing narrower at the processus. I aspirated this swelling and dressed the bag with double flannel expressed from hot claret. In an effort to prevent recurrence, a strong decoctum of Coct. Querc.* was applied in order to strengthen the relaxed fibres and purse up the tunica, so lately under the preternatural dilatations, and if possible to prevent more of the same liquor from extravasation. I likewise purged him, once a week, with a spoonful of Tinct. sacra overnight and half a drachm of Pulv. Jalapae in the morning, with hopes of keeping the serous illuvies or to divert the course the other way. The patient returned nine months later, was offered castration but refused."

Sixteen years later James Handley claimed that all aequous tumours were due to a superfluity of serum in the blood, and gives a good clinical description of these tumours. "It is sometimes less, sometimes more, yields when it is hard pressed, it is not painful and does not pit, and is attended with an itching in the part by reason of the saltness of the tumour. If they lie externally, they appear resplendent and if they be deeper and are shaded by the hand and a candle in a darkened room a faint transparency may be seen." As for the treatment of hydrocele, he stated that diet, internal medicines and external applications should be attempted but should operation be necessary it should be by the use of simple incision or by the use of caustics, (Fig. 2). The diet he recommended was as follows:—"Roast meat rather than boiled, shun all immoderation in drink, flesh is better than fish." Internal medicines were devoted towards purging by stool, urine or sweat. A number of external applications included cataplasms of Fol. Malv., Favin. Lupinoi, Ol. Anethi, Cham. vin Alb., mustard, nettle seed, brine and Ammoniacum‡. Finally after operation he sug-

*Quercus—Oak Bark—Quercus Pedunculata—Dried bark and small branches.

‡Ammoniacum: A gum resinous exudation from the stem of Drauna Ammoniacum; Collected in Persia and the Punjab. Forms a milky emulsion in water.

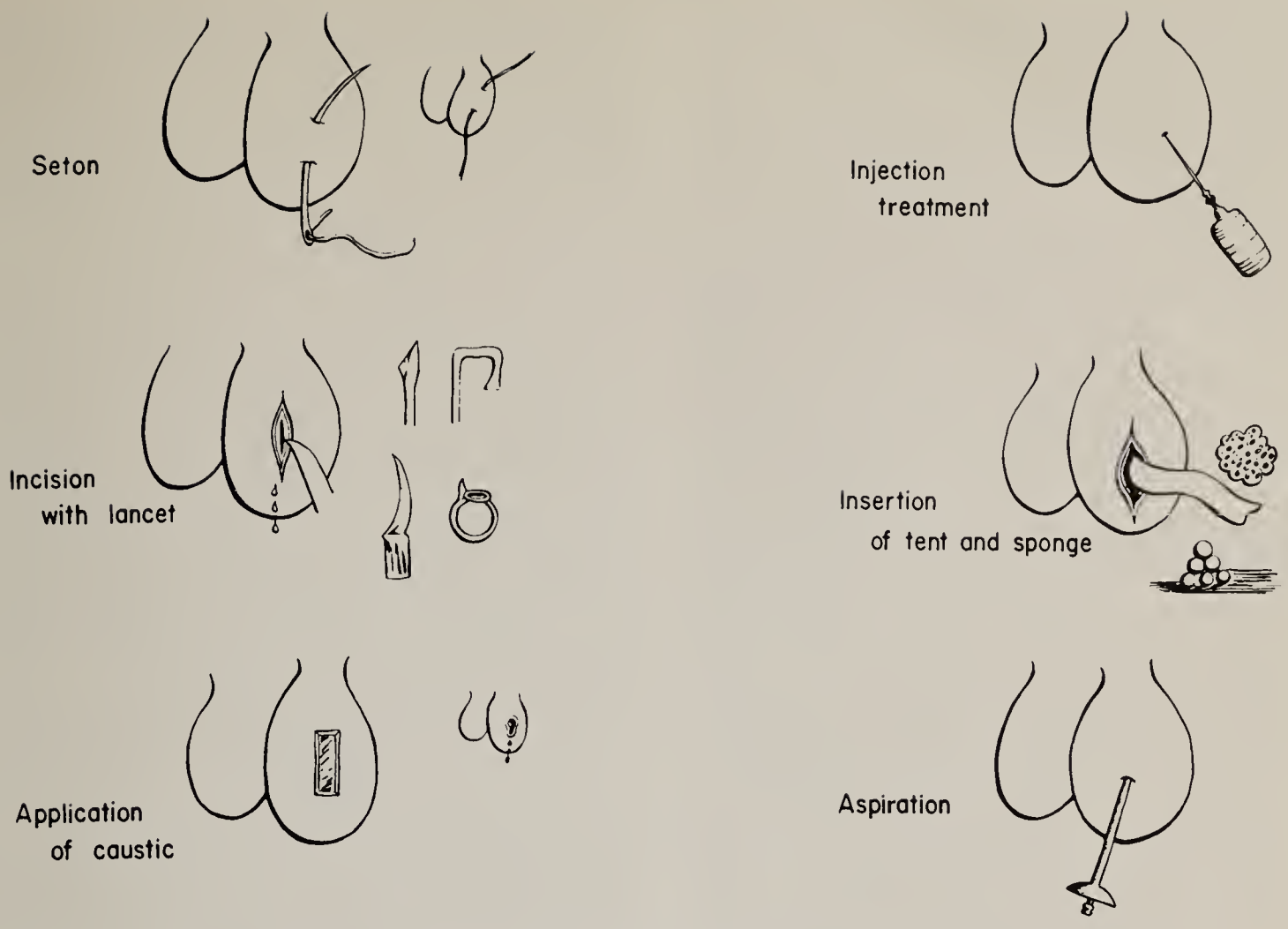

Fig. 2.—Illustration to show the methods of treatment of hydrocoele of the tunica vaginalis.

gested that the wound be kept open with a tube of lead or silver.

In 1779 Samuel Sharp, a surgeon at Guys Hospital in London, noted that some hydroceles once formed remained static yet others formed more rapidly. He disbelieved that the fluid was due to 'waters falling from the belly'. He found that internal medicine and external applications were of no help but recommended that should treatment be necessary, it should be by means of a lancet rather than with a trocar. Here is an extract from one of his case histories on January 3, 1736:—"After emptying the tunica vaginalis I injected one ounce of spirit of wine, the patient experienced great pain. The following day the teguments were thickened, this was followed by increase in the size of the swelling and much pain. Ultimately two abscesses discharged one month later. Cure resulted by the adhesion of the testis to the tunica vaginalis."

John Hunter (Fig. 3), (1728-1793) wrote at considerable length on this

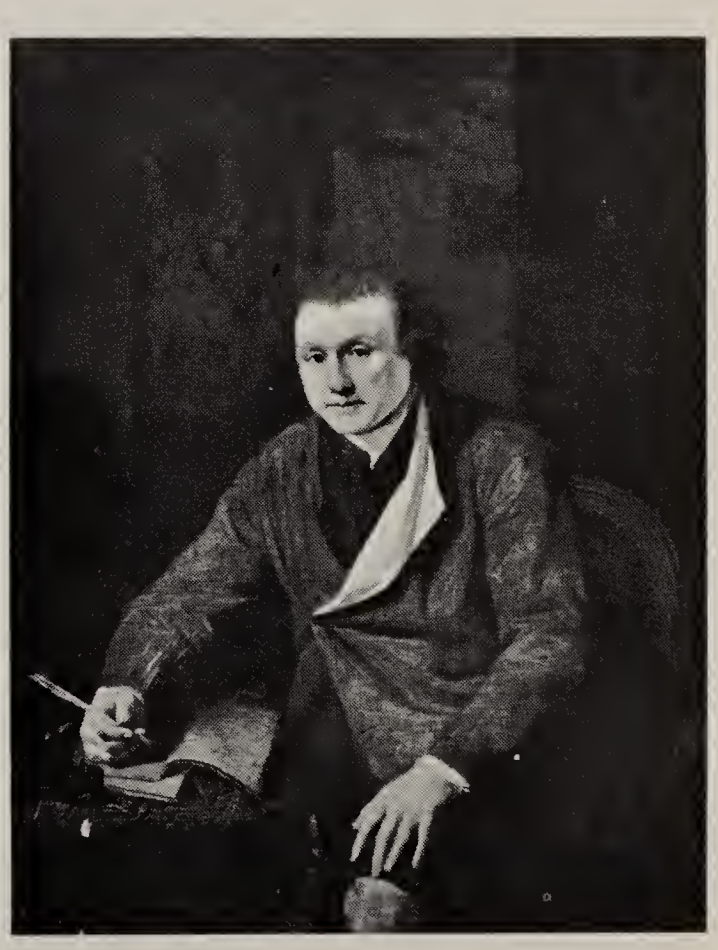

Fig. 3.—John Hunter 1728-1793 aged about 40—by Robert Home. Original painting in the Royal College of Surgeons of England.

subject and mentions that hydrocele can be confused with cysts of the epididymis. He made the observation that hydrocele was more common in warm climates and that it may be secondary to underlying disease of the testis. Paracentesis was recognised by Hunter as being a temporary cure, but if after this procedure inflammation should set in, a radical cure could be effected. He quotes Dupuytren's words on the subject of hydrocele: "Operations of convenience much more frequently prove fatal than others, surgeons occasionally allow themselves to be persuaded by the importunities of the patient to undertake operations against which their own judgments loudly declare. Surely such conduct ought to be reprobated as proceeding either from culpable weakness or some motive still more reprehensible." Hunter believed that radical cure rested with inflammation, suppuration and granulation but suggested that hydrocele should be aspirated before attempting a radical cure to exclude disease of the testis. Methods by which inflammation could be caused were by no means new, the seton, the tent, and injections of various substances had all been tried with appraisal. His own method which he claimed as successful, was responsible for a number of deaths. His particular method of treatment is as follows:— "Incise the scrotum, three inches in length and let the whole water escape. Then fill it as full as possible with pretty stiff poultice (occasionally introducing your finger to direct your poultice) into every corner of the bag and lastly put some lint into the wound to keep the poultice in. The poultice should be made of linseed meal, made into little balls it will be more convenient . . . inflammation becomes universal, the poultice does not become entangled with granulations, the parts granulate and contract and gradually squeeze out the poultice.) To prevent inflammation coming on too quickly and causing unnecessary pain, a linen cloth soaked in brandy and squeezed dry is applied to the scrotum."

John Douglas (1755) wrote a treatise on hydrocele from the experience he had gained whilst in Barbados. He came to the conclusion that this disease affected people of weak and relaxed habit, but that trauma such as that occasioned by a kick or bruise on the pummel of a saddle may cause it. He was the first to state that the left side was thought to be the most often affected. He recommended treatment for the following reasons: "A hydrocele is troublesome in that it causes the patient to straddle, to be unable to walk or ride in comfort and as the penis is quite buried, procreation is rendered difficult. These inconveniences give rise to lowness of spirit." He advocated excision of the tunica vaginalis as being the only satisfactory radical cure.

So far the theories on formation of the hydrocele fluid have rested with excess of the appropriate humours, a superfluity of serum, weakness of the integuments of the scrotum and descent of fluid from the abdomen. Trauma and disease were also recognised as a cause. Percival Pott (1765) gives a reasoned approach to the aetiology of hydrocele in his manuscript on this subject: "An obstruction in the lymphatic vessels of the spermatic cord may in some degree prevent the regular and due absorption of the fluid from the tunica vaginalis. That if more of the fluid be deposited than the absorbant vessels can take up, or if the absorbant vessels do not execute their office, such fluids must be accumulated within the cavity of the said tunica." Pott agreed with John Hunter that the only rational treatment was by producing cohesion between the two tunics and that inflammation would give the desired result. Pott used the seton and caustics, 'said to spare the terror which cutting instruments conveyed'.

Thomas Keate (1788) wrote that, 'We have not yet reached the *ne plus ultra* in the treatment of hydrocele'. He claimed beneficial results from the powerful desutient properties of sal ammoniac used topically when dissolved in water with the addition of spirit of wine and vinegar.

Two years later James Earle proposed

the injection of 'du vin du Porto' mixed with a concoctum of red rose leaves. This produced a mild inflammation causing adhesion between the testis and the tunica vaginalis.

Sir Astley Cooper (1830) considered that the cause of hydrocele was due to the relaxation of the capillaries of the tunica vaginalis, with the exudation of a large quantity of fluid which resembled serum. He believed that the *modus operandi* of acids and alcohols, zinc sulphate, and port wine in being effective in the cure of hydrocele rested with the fact that these substances produced coagulation of the hydrocele fluid. He used milk in an attempt to try to suppress reformation of the fluid but desisted as the fluid returned curdled. He recommended the use of a seton in children.

At this time the famous historian, Gibbon died from the complications of a hydrocele of enormous dimensions. Altogether twenty-six pints were removed.

In 1850, William Fergusson, a surgeon at Kings College Hospital, London, enumerated the substances which had previously been used by injection for the treatment of hydrocele. 'Solutions of salts of alum, acetate of lead, sulphate of copper, corrosive sublimate and other kinds of lime water, acids of alcohol and various tinctures and infusions of roses and oak bark.' He gave credit to Mr. Martin of Grosvenor Street in 1841 as being the first to introduce the injection of Tincture of Iodine* as a method of radical treatment.

Samuel Osborn in 1878 adopted the following classification for hydrocele: I. Hydrocele of the tunica vaginalis may be visceral or parietal. II. Hydrocele of the whole vaginal process, which is necessarily congenital. III. Hydrocele of the funicular portion of the vaginal process of peritoneum which may be congenital or acquired.

It was becoming recognized that there normally exists a turnover of the fluid retained within the tunica vaginalis. Mr. Curling at The London Hospital in 1843 was the first to analyse hydrocele fluid. He found it to contain water 91.25%, albumin 6.85%, uncoaguable matter 1.1%, salts 0.8%.

Diseases listed as responsible for causing hydrocele were, epididymitis, syphilitic orchitis, and cancer of the testis. It is interesting to note that though Osborn was a believer in the phenomenon of relaxed arteries of old people, he also thought that trauma or irritation caused by loose bodies composed of cartilage, consequent on rupture of the hydatids of Morgagni. He mentioned that the presence of a hydrocele may lead to suppression of spermatogenesis. He treated the old with simple tapping but thought scarification of the tunica vaginalis with a cannula and local application of the tunica vaginalis with a cannula and local application of silver nitrate was helpful.

In Italy, attempts were being made to cure the hydrocele by the use of electricity. The negative pole of a battery was connected to the inner surface of the tunica and the positive pole to the skin of the scrotum. This method of treatment was soon discontinued. Iodine, carbolic acid and glycerine were all tried though it was discovered that setons soaked in iodine caused much suffering to the patient.

In 1888, Morris stated that there was still no safe cure for the hydrocele. Sir Frederick Treeves at The London Hospital adopted the practice, in cases where injection treatment had failed, of opening the tunica vaginalis and swabbing it out with pure carbolic acid. On injection therapy he wrote: "The time honoured treatment is on the whole very successful when properly performed. The most preferable are carbolic acid and linamentum iodi. Caroblic acid poisoning, cellulitis of the scrotum, sloughing and suppuration of the sac may follow."

The treatment of hydrocele by 'Autoserotherapy' was advocated by Gilbert in 1894. Two cubic centimetres of hydrocele fluid were removed and injected beneath the skin. After a second injection he claimed that the hydrocele disap-

*Tincture of Iodine, Iodine ½ oz., Iodide of Potassium, Rectified spirit—1 pint.

peared. These results were not reproducible so the treatment was discontinued.

It can be seen that at the turn of the century there was no really safe or satisfactory cure for this condition. The aetiology was still undiscovered. At the present time palliation is still used in the elderly, though surgery offers a radical cure with minimal discomfort to the patient. Until a cause is found for this condition, the pens of surgeons may continue to add to the knowledge of this interesting condition.

ACKNOWLEDGEMENTS

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ABSTRACTS AND REVIEWS

OF PUBLICATIONS BY THE STAFF

Gout in Infancy Manifested by Renal Failure. I. M. Rosenthal, S. Gabballah, and M. E. Rafelson, Jr.: *Pediatrics, 33, 251-257, 1964.*

A case of gout in a male infant manifest at the age of 7 weeks by signs of renal failure is reported. The child recovered after alkalinization of his urine increased the solubility of precipitated uric acid in the renal tubules. Evidence for gout was found in the maternal and paternal sides of the family. A metabolic study employing N^{15}-labeled glycine demonstrated increased incorporation of glycine into uric acid of the same magnitude previously found in some adult patients with gout.

Experimental Homotransplantation of the Lungs with Cytoxic Agents. P. Parsa, L. P. Faber, E. W. Staub, and E. J. Beattie, Jr.: *Diseases of the Chest, Vol. 45, No. 4, April, 1964.*

Lung homotransplantation was performed in 16 paired dogs. Methotrexate and Imuran were used to prolong the survival time. In the group of dogs treated with methotrexate, the average survival was 15 days, and no dog revealed evidence of the transplanted lung by bronchospirometry. In the group of dogs treated with Imuran, the average survival was 27 days, with evidence of relatively normal pulmonary function in at least one dog, two months following surgery. In this dog, there was no evidence of graft injection. Death occurred from aspiration pneumonitis in the normal lung.

Isolation and Characterization of a New Herpes Virus. A. W. Holmes, R. G. Caldwell, R. E. Dedmon, and F. Deinhardt: *J. Immunol, 92: 602-610, 1964.*

A new virus has been isolated from marmosets dying of generalized disease. This agent satisfies the chemical, physical, biological and immunologic criteria for inclusion in the group of herpes viruses. The reservoir of this virus in nature is not known but it is not likely to be the marmoset. The temporary designation of herpes M or Herpesvirus tamarinus is suggested for this agent.

Indications for Sympathetic Blocks. J. A. Hunter, H. Najafi, and O. C. Julian: *Surg. Clin. No. Amer., 44:81-89, 1964.*

Temporary sympathetic denervation has a wide variety of uses, both in treatment of pain or vasoconstriction and in diagnosis. Diagnostically, the procedure differentiates between severe arterial spasm and obscure traumatic occlusions. In therapy, sometimes with concurrent diagnostic value, blocks are indicated in causalgia, in vasospasm of early thrombophlebitis with impending phlegmasia cerulea dolens, and in reflex arterial constriction accompanying embolism. Other less frequent but occasionally important uses are stellate ganglion block in acute intracranial arterial occlusion, dorsal ganglion block or ganglionectomy in intractable angina pectoris, and splanchnic biliary dyskinesia, and some forms of ureteral colic.

Treatment of Pain. Causalgia or posttraumatic sympathetic dystrophy is suspected when a burning pain in an extremity, inappropriate to the initial injury, persists. If the pain does not resolve spontaneously, diagnosis is confirmed and striking relief obtained by sympathetic ganglion block. If pain recurs, the block may be repeated two or three times before surgical sympathectomy is indicated. In deep thrombophlebitis of lower extremities, early reflex vasoconstriction is common. Lumbar sympathetic block with procaine hydrochloride may bring rapid relief of pain and interrupt severe vasoconstriction reflexes which otherwise lead to phlegmasia cerulea dolens. In acute cerebrovascular

occlusion, a stellate block soon after onset often brings temporary improvement; a favorable response is indication for repeated blocks. Sympathetic blocks must be considered dangerous in patients under anticoagulant therapy, however. Stellate ganglionectomy is never indicated for acute cerebrovascular occlusion; depressed circulation attending the procedure is considered far more damaging than possible improvement is worth. Little use is made of sympathetic blocks in treatment of visceral pain or angina pectoris because of unreliability of results and existence of preferred treatment.

Treatment of Vasoconstriction. In vascular constriction resulting from arterial embolism, blocks of the lumbar or dorsal sympathetic chain may help locate the level of the embolus by eliminating the spasm that makes evaluation of pulse and interpretation of skin color and temperature changes difficult. Preoperative sympathetic block may detect embolic material lodged distally. Also, restoration of some blood flow helps avoid intra-arterial thrombosis in the periphery. In arterial injuries with no external hemorrhage or blood loss into tissue, procaine blocks help differentiate anatomic occlusion. Management depends on evaluation of all physical findings. However, a procaine block may effect some limb restoration and almost always obviates the need for arteriography or surgical exploration without definitive diagnosis. Sympathetic blocks also are of some aid in chronic arterial occlusion, although diagnostic reliability is questionable and decision to use sympathectomy depends on many other clinical criteria.

Management of Hepatic Coma. P. N. Jones and R. B. Capps: *Med. Clin. N. Amer. 48:37-51, 1964.*

Successful management of patients with severe liver disease requires supportive therapy, prevention of further injury to the liver, and avoidance of conditions provoking hepatic coma. Factors precipitating coma include liver failure, gastrointestinal hemorrhage, cholemia, certain drugs, surgery, protein intolerance, intercurrent infection, and paracentesis. The syndrome includes a precoma stage without loss of consciousness and often one of deep coma. Duration is usually four to five days, but coma may last two weeks in some patients with prolonged hyperbilirubinemia. Onset is indicated by confusion, inappropriate behavior, thick speech, apathy, drowsiness, and occasionally agitation and delirium. Hyperreflexia, rigidity, and flapping tremor occur. In deep coma, extremities are flaccid and areflexia appears. Clinical diagnosis is aided by an electroencephalogram.

Factors depressing liver functions include anoxia secondary to hemorrhage or use of narcotics, intercurrent infection, exercise, late pregnancy, and abdominal paracentesis. Oxygen is given to patients in either coma or precoma stage. Narcotics and sedatives are used sparingly. In amounts of 25 mg., promazine (Sparine) is given every four to six hours for agitation and meperidine (Demerol) every two hours for postoperative discomfort. Gamma globulin is indicated for exposure to infections or serum hepatitis. Antibiotics are used for bacterial infection, fever or diarrhea is controlled, and complete bed rest is ordered. Labor is induced at onset of coma if the pregnant patient fails to begin spontaneous labor. Only minimal amounts of fluid are removed if abdominal paracentesis is necessary.

Gastrointestinal hemorrhage increases ammonia in the colon and may precipitate coma. Ingestion of proteins or ammonia salts increases ammonia toxicity. Dietary protein and drugs containing ammonia are eliminated until coma clears. Ammonia-producing bacterial ureases are reduced with nonabsorbable antibiotic or sulfa drugs. Hemorrhage must be controlled and colonic blood removed by repeated enemas. If possible, only fresh blood should be used in transfusion. Thiazide diuretics and acetazolamide increases renal production of ammonia and are contraindicated. Hypokalemia should be prevented. Minimal oral protein intake is recommended for patients with shunts resulting in extensive portal-collateral circulation. Severe, protracted hyperbilirubinemia often associated with prolonged coma should be treated with steroids. Supportive therapy consists of careful nursing care, blood transfusions, and vitamin preparations, including vitamin K, daily. Elective surgery should be postponed. Only essential medication, nontoxic to the liver, should be used.

Observations are based on treatment of 82 patients with 98 episodes of hepatic coma.

Development of an Attenuated Mumps Virus Vaccine I. Determination of neutralizing serum antibodies against mumps virus. F. DEINHARDT and G. SHRAMEK: *Journal of Immunology, Vol. 93, No. 3, pp. 462-465, Sept. 1964.*

This neutralization test, using inapparent infection of L cells by mumps virus and resulting interference phenomena as an assay system for the evaluation of neutralizing serum antibodies against mumps virus, has proven simpler and more rapid and accurate than previous test systems. It has been shown that the VSV challenge dose and the time of challenge can be varied over a wide range without altering the test results. The actual amount of mumps virus present in each individual test is less critical than in the previously described CPE or HA test, and the reading of an all-or-nothing effect of the challenge virus takes less time and is more objective than the grading of a partial CPE or hemadsorption. The L cell interference test has been used in this laboratory in studies on vaccination against mumps virus for about a year and has proven to be a reliable and accurate simple serologic tool for routine use.

A similar test system has recently been reported for rubella virus and similar test systems may lend themselves to the development of simple and accurate tests both for the evaluation of growth characteristics and for the determination of serum antibody titers against those viruses which do not exhibit definite cytopathic or chemical changes in infected tissue cultures.

Inhibition of Interferon Production by 5-iodo-2-deoxyuridine. A. W. HOLMES, J. GILSON and F. DEINHARDT: *Virology, Vol. 24, No. 2, pp. 229-232, Oct. 1964.*

The effect of different concentrations of IDU on interferon production has been shown to be similar to the effect of the same concentration on cell multiplication, i.e., definite inhibition of both cell multiplication and interferon production was observed with IDU concentrations of 3×10^{-4} *M* or higher and little or no effect with IDU concentrations of 3×10^{-5} *M* or lower. On the other hand 3×10^{-3} or 3×10^{-4} *M* IDU did not inhibit the multiplication of RNA viruses.

The halogenated pyrimidines are known to be potent inhibitors of DNA replication and it has been shown that at least for short periods of time the replication of DNA can be completely abolished by 5-fluorodeoxyuridine without interfering with the RNA metabolism of tissue culture cells. Higher concentrations of IDU are needed to obtain the same effect as measured indirectly by evaluation of multiplication of tissue culture cells and of RNA and DNA viruses. It is therefore suggested that formation of new DNA is essential for interferon production.

The Human Urinary Bladder Mucosa. An Electron Microscopic Study. H. BATTIFORA, R. EISENSTEIN, and J. MCDONALD: *Investigative Urology, 1:354-361, 1964.*

During the course of an ultrastructural and biochemical study of human bladder neoplasms, the normal bladder mucosa was studied in thirteen patients without bladder disease. The human bladder mucosal cells are characterized by their ultrastructural simplicity. The most prominent cytoplasmic structures are numerous smooth surfaced vesicles of pinocytotic origin. Other organelles are less conspicuous. Short and sparse microvilli are present on the surface cells. The deeper cells have frequent nuclear membrane invaginations. A system of intercellular spaces that seemed to enlarge with exposure to distilled water is seen. Pinocytotic vesicles are present in the lateral walls of the cells in connection with these spaces. A continuous basement membrane was demonstrated. The role of the intercellular spaces in the transport of water and solutes is discussed. The ultrastructural simplicity of the bladder mucosal cells makes them especially suitable for electron microscopic studies of the changes which accompany the transitions characterizing the various stages of neoplasia.

The Relation of Coagulation Factor Defects to Surgical Blood Loss. J. H. Olwin, and J. L. Koppel: *Ann. N. Y. Acad. of Sci. 115: 43, 1964.*

The paper discusses bleeding problems which may confront the surgeon, particularly those related to coagulation factor deficiencies. It describes methods for identifying hemostatic abnormalities present in the patient prior to, as well as developing unexpectedly during, surgery and outlines methods of treatment for the various deficiencies.

From the available information concerning the survival of transfused clotting factors in vivo and their preservation and stability in vitro, the following conclusions can be drawn:

1) Fresh plasma of whole blood, within 12 hours of collection in citrate, is the preferred treatment in cases of classical hemophilia and those with Factor V deficiency.
2) Bank blood or plasma, preferably within 20 to 30 days of collection, can be used in patients with hypoprothrombinemia, deficiencies of Factors VII and X, PTC and PTA and those with fibrinogenopenia.
3) Fresh or stored serum is effective in the treatment of deficiencies of Factors VII, X, and PTC.
4) Whole blood should be used only when necessary to correct anemia due to severe blood loss or where such loss can be definitely anticipated.
5) The indiscriminate use of blood or plasma transfusions in patients with bleeding tendencies should be discouraged, particularly when it is intended to prevent, rather than arrest hemorrhage.

The Effect of Phosphatidyl Choline on the Degradation of Phosphatidyl Ethanolamine by the Phospholipase of Post-Heparin Plasma or Snake Venom. W. C. Vogel, J. L. Koppel and J. H. Olwin: *J. Lipid Research 5: 385, 1964.*

The degradation of phosphatidyl ethanolamine by human post-heparin plasma phospholipase is not significantly affected by phosphatidyl choline added to the assay system as an aqueous emulsion. However, when the two phospholipids are combined in chloroform-methanol and the solvent is removed prior to their joint emulsification, a marked reduction of phosphatidyl ethanolamine degradation is observed. The extent of this reduction is dependent upon the relative amount of phosphatidyl choline added. The results obtained are interpreted on the basis of a hypothetical complex formation between the two phospholipids.

A comparison of the phospholipase activities of human post-heparin plasma and Crotalus adamanteus venom reveals both similarities and differences in the behavior of the two enzymes.

Interaction of Bovine Autoprothrombin C with Phospholipids and Divalent Cations. E. R. Cole, J. L. Koppel and J. H. Olwin: *Can. J. Biochem. 42: 1595, 1964.*

A thromboplastic enzyme, autoprothrombin C, can be complexed to different phospholipids and removed from solution in the form of such complexes. A technique for dissociating these complexes was developed, resulting in the recovery of the thromboplastic enzyme essentially free of phospholipid and in a higher degree of purity. Calcium ions are required for the formation of the complex, but strontium can replace calcium not only as the metal ion in the phospholipid-complexing system, but also as an autoprothrombin C cofactor in a prothrombin activation mixture. Magnesium was not effective in either system.

The role of different phospholipids in the complexing phenomenon was studied and compared with the suitability of the same phospholipids as prothrombin-activating cofactors of autoprothrombin C. All phospholipid preparations studied complexed with autoprothrombin C to some degree, but the most efficient complexing agents were found to be asolectin and a commercial phosphatidyl ethanolamine preparation, both materials being among the ones which demonstrated the highest prothrombin conversion activity. Since thrombin was not complexed under the same conditions, autoprothrombin C could be isolated from commercial thrombin preparations also containing autoprothrombin C.

Vitamin D-Induced Aortic Calcification. R. Eisenstein and L. Zeruolis: *Arch. of Path., 77:27-35, 1964.*

In the calcific arterial disease induced by hypervitaminosis D, there are two morphologic components, a newly-formed cellular intimal cushion and a medial calcific mass. The cells comprising the intimal cushion are primarily smooth muscle cells which presumably are involved in the synthesis of the stroma of the plaque. Although elastic tissue appeared to be the first structure to calcify, all the structures in the media eventually calcified. There were local variations in crystal size and habit and in the susceptibility of the media to calcification which are not explained but which are apparent in electron micrographs. The newly-formed cellular intimal cushion over the calcified media did not calcify.

Actinomycin D Inhibits Parathyroid Hormone and Vitamin D Activity. R. Eisenstein and M. Passavoy: *Proc. Soc. Experimental Biology and Medicine, 117:77-79, 1964.*

Actinomycin D inhibits the hypercalcemia induced by large doses of parathyroid extract or vitamin D. It also alters the bone changes induced by these agents. The data thus indicate that these agents may act by inducing synthesis of new enzymes in bone induced by DNA directed RNA which in turn enzymatically degrade bone.

Interferon Production In Vitro by Cells Infected with the Murine Salivary Virus. D. Henson, and R. D. Smith: *Proc. Soc. Experimental Biology and Medicine, 117:517-520, 1964.*

In mice infection with the murine salivary gland virus (MSGV) characteristically results in a chronic inapparent infection evidenced by the presence of intranuclear inclusions and persistent demonstrable virus in the salivary glands. On this basis it seems, therefore, that MSGV can be utilized to investigate latent asymptomatic viral infections. Initial attempts to define the host-virus relationship have resulted in the demonstration of a viral interfering substance produced in vitro and having many properties similar to those of interferon. Using encephalomyocarditis virus (EMC) in "L" cells as a heterologous virus-cell test system, an EMC inhibiting substance was detected in the growth media from mouse embryo cell cultures infected with MSGV. The interfering substance was non-dialyzable, heat-labile at 60° C for one hour, stable at pH 2, not affected by MSGV antiserum and was not sedimented at 90,000 x g. In infected cultures, the rise in MSGV titer was associated with a corresponding rise in the interferon activity.

Human Cytomegalovirus: Intranuclear Virus-Synthesizing Bodies. H. Pinkerton, C. H. Sun, D. Henson and J. Neff: *Virology: 24:498-500, 1964.*

Microscopic examination of tissue culture cells infected with the human cytomegalovirus revealed during early stages of infection the presence of numerous small, 0.5—1.5 micra, spherical bodies within the nucleus. Electron microscopic study revealed such intranuclear bodies to be viral-synthesizing bodies consisting of an electron dense matrix in which many incomplete and complete virions were present. In presumed later stages, the spherical bodies were composed of skeins of very electron dense anastomosing strands with large numbers of maturating virions in the interstices. Definite peripheral membranes enclosed many of these bodies, especially in later stages. These bodies are of particular interest because of their location within nuclei and because they are apparently concerned with the assembly of a DNA containing virus.

Antinuclear Antibodies in Families of Patients with Systemic Lupus Erythematosus. V. E. Pollak: *New Engl. J. Med. 165-171, 1964.*

Antinuclear antibodies were found in 91.5 per cent of serum samples from patients with systemic lupus erythematosus and in 25 per cent of patients with rheumatoid arthritis and other collagen diseases. They occurred in only 4 per cent of 271 patients with diseases

other than systemic lupus erythematosus and the collagen diseases, and in none of 71 healthy subjects.

Antinuclear antibodies were found in relatives of patients with systemic lupus erythematosus in 25 of 43 families studied. In all, positive tests were found in 33 per cent of 142 first-degree and 21 per cent of 47 second-degree relatives. They were not detected in serum specimens of 24 relatives of matched healthy subjects.

These observations strongly suggest that hereditary factors are important in the production of antinuclear antibodies.

A Critical Evaluation of the Indirect Basophil Degranulation Test. J. R. Bobitt, H. Schechter, and V. E. Pollak: *Proc. Soc. Exp. Biol. Med. 117:608-610, 1964.*

Degranulation of basophils *in vitro* has been claimed to be a simple test for the detection of antibody. In this study the indirect basophil degranulation test was evaluated by replicate "blind" analyses of 8 sera from healthy subjects and penicillin sensitive and ragweed sensitive subjects. Ragweed and penicillin G were used as antigens. The results indicate that degranulation of basophils is a random phenomenon which was not influenced significantly by the presence or absence of the antigen in the test system or by the presumed presence or absence of the antibody in the serum.

Quantitative Histochemistry of the Nephron IX. Distribution and Activity of Various Enzymes in the Kidney of the Dog. H. Mattenheimer, V. E. Pollak, and H. DeBruin: *Enzymol. biol. clin. 4:107-120, 1964.*

The optimum conditions for the measurement of the activities of lactate dehydrogenase, malate dehydrogenase, glutamate dehydrogenase, alanine aminotransferase, aspartate aminotransferase, carbonic anydrase, D-alanine oxidase, citrate synthase, and the glutaminases were investigated in the dog kidney.

The activities of these enzymes were measured in the glomeruli, proximal and distal convolutions, and medullary rays dissected from 16μ lyophilized sections of the dog kidney. The results were compared with the activities in homogenates of the cortex.

The Fascinating Lady Mary Wortley Montagu. E. L. Strohl: *Archives of Surgery, Vol. 89, pp. 554-558, Sept. 1964.*

Lady Mary Wortley Montagu (1689-1762), beautiful, intellectual and witty, can be credited with the first employment, in England, of inoculation against smallpox, having antedated Jenner, who was born in 1749, and made his vaccine discovery in 1796.

Of patrician heritage and high social position, she was a serious student, having acquired facility in Latin, self-taught, and when twenty-one years old made a translation from Latin to English of Enchiridion of Epictetus.

Her beauty and intelligence attracted Edward Wortley Montagu, a grandson of the Earl of Sandwich; however, the romance, discouraged by her father, resulted in elopement, Lady Mary bringing as dowry a nightgown and petticoat.

Their trip to Constantinople, where her husband was appointed Ambassador, provided many observations, which she recorded, and in one of her letters she described the practice of "ingrafting" carried on by old women in Adrianople, Turkey, as a successful preventive of smallpox; so successful that she allowed the "ingrafting" on her own son.

Her sponsorship of the practice in England, on their return, brought criticism and abuse from all circles—scientific, ecclesiastical, and the public, but after its success was demonstrated, she was highly praised by these same groups.

During her later life in many European countries, comprising twenty years, she was revered for her benevolence and humanitarianism, and after her return to England, and death in 1762, a centograph, erected in her memory by Henrietta Inge, in 1789, still stands in the cathedral at Litchfield as an everlasting tribute to this valiant woman.

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MILD DIABETES AND PREDIABETES:
Response of the Hypoglycemia to Tolbutamide

Peter G. Economou, M.D.[1]
Will G. Ryan, M.D.[2]
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INTRODUCTION

Symptomatic hypoglycemia as a manifestation of early diabetes has been well documented by several investigators[1–4]. Seltzer, Fajans and Conn[1] were the first to report a large number of patients who were clearly diabetic but who also exhibited a late hypoglycemic phase when exposed to an oral glucose load. Sixty-nine per cent of their 110 patients had complained of post-prandial hypoglycemic symptoms. In our experience, clinical hypoglycemia may also occur in what has been referred to as prediabetes[5,6,7]. By prediabetes, we mean those individuals who are not overtly diabetic and whose oral glucose tolerance test (O.G.T.T.) is normal or shows only borderline abnormalities. These individuals, however, often have a strong family history of diabetes or the prediabetic state may manifest itself as glycosuria during pregnancy, large birth weight of the individual or her children. In addition, stresses such as infection, trauma or cortisone therapy may induce a temporary diabetic state[8]. In all the above circumstances, the impaired glucose tolerance may be temporary and initially may return to normal, but generally permanent diabetes eventuates.

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The symptoms of hypoglycemia with early or prediabetes usually occur 3 to 5 hours after a meal and a 5 hour O.G.T.T. will usually disclose this condition. Often, the symptoms of hypoglycemia will be noted during the test procedure.

The hypoglycemia seen in these patients may, at first hand, seem somewhat paradoxical since it may be the only manifestation of early diabetes. However, there is convincing evidence that this early phase of diabetes mellitus may also progress to overt diabetes with persistent fasting hyperglycemia and a loss of the hypoglycemic element[1]. Furthermore, the investigations of Yalow and

Berson[9] have tended to resolve this paradox. These investigators have shown that in non-diabetic subjects, the plasma insulin level during an O.G.T.T. reaches a peak during the first half hour. Following the first hour, instead of a decline as noted in non-diabetic subjects, there is a continued and significant rise in plasma insulin. In view of these findings, one might postulate that the hypoglycemia seen in our patients stems from a lag in the speed of mobilization of insulin in response to the glucose load. Because of this initial delay in insulin secretion, the resulting hyperglycemia now affords a super-normal stimulus to the Islets of Langerhans during the third to fifth hours with ensuing hypoglycemic symptoms.

It occurred to us that in patients with early diabetes or prediabetes associated with hypoglycemia, tolbutamide therapy, which apparently stimulates the release of endogenous insulin[10,11,12], might prevent the initial lag in insulin secretion and, perhaps, circumvent the late rise. To rephrase the problem, if the early hyperglycemic phase of an O.G.T.T. could be prevented with tolbutamide, would the later hypoglycemic phase be obliterated?

It is the purpose of this paper to present findings in patients in whom hypoglycemia resulted from the early or prediabetic state and to describe our preliminary results with tolbutamide therapy.

MATERIALS AND METHODS

The subjects examined in our study were 10 females and 11 males, the ages ranged from 27 to 72 years. All subjects, with the exception of one, were hospitalized when the diagnosis of prediabetic hypoglycemia was made. As a group, these patients were distinguished by the following essential features:

1. All had clinical symptoms highly suggestive of hypoglycemia occurring several hours post-prandially. These included irritability, weakness, hunger, sweating, marked fatigue, giddiness, sleepiness, numbness, and, in addition, convulsive episodes occurred in two patients during the later phases of the O.G.T.T.

2. All patients were found to have blood sugar values of 65 mg.% or less after the second hour of the O.G.T.T. (Table I).

3. All 21 subjects had abnormalities suggestive of diabetes mellitus in one or more of the following procedures (Table I):

a. **Oral glucose tolerance test (O.G.T.T.).** A solution containing 100 gms. glucose (Dextal, Scientific Products) was ingested during a 5-10 minute interval. Venous blood was obtained in the fasting state and after ½, 1, 2, 3, 4, and 5 hours after glucose administration. The criteria employed for interpretation are those of Fajans and Conn[13], i.e., the upper limits of normal were taken as 160 mg.% at one hour and 110 mg.% at two hours.

On those occasions when this procedure was repeated following the institution of treatment, tolbutamide therapy was continued up to and including the morning of the test.

Both clinical and biochemical evaluation was attempted. In all instances, one or more of the authors in addition to the referring physician reappraised the clinical status of the patient. The O.G.T.T. was also used in an effort to provide objective documentation of the patient's status when this procedure was performed.

b. **Intravenous glucose tolerance test (I.V.G.T.T.).** Fifty ml. of 50% glucose in water were given intravenously over a 3-4 minute period. Following the completion of the injection a total of 6 specimens of blood were taken at 10 minute intervals. The rate of disappearance of glucose (**K**g) was determined a modification of the technique of Amatuzio et al.[14] **K**g (% decrease per minute) was determined by plotting the blood sugar values against time on semilogarithmic paper. Lines were fitted to these points by visual inspection. In our laboratory, **K**g values of 1.15 or more are considered normal, while a value

Table 1—Clinical and laboratory data on 21 patients with symptomatic mild or prediabetic hypoglycemia.

Name	Age Color Sex	Total Months Rx	OGTT F	1/2	1	2	3	4	5	Tolbutamide Amt. Gms.	Mos. Rx	IVGTT (Kg)	TRT (% of fasting) 20	30	45	60	F.H. of D.M.	Remarks
H.L.	46,W,M	19	87	159	149	153	103	58				0.73					Yes	Glycosuria prior to therapy.
			77	181	197	161	117	50	58	1.5	15							
			71	186	220	197	137	45	56	2.0	2							
W.D.	39,W,M	18	90	195	175	109	35	64				1.14	79	86	80	70		Minimal glycosuria prior to therapy.
			90		152	100	65	64		1.5	11							
G.S.	34,W,F	16	104	220	242	208	121	70	65			0.72	87	71	64	52		Glycosuria during pregnancy.
			105	177	226	174	116	83	55	0.5	11							
R.W.	34,W,M	14	110	170	148	110	59	67										
			88	154	200	138	86	61	66	1.0	9	0.89	85	84	78	72		
J.G.	27,W,M	14	94	198	232	117	55	47	50			0.73	88	86	83	69		Glycosuria on two occasions in 1956.
			83	114	145	108	45	54	66	1.5	9							
			93	155	137	137	65	64	73	1.5	5							
M.H.	50,W,F	11	82	185	173	131	24	65				1.39	85	91	85	85	Yes	
			76	162	150	51	79	66	69	0.5	7							
N.S.	46,W,F	9	88	153	166	160	63	94	105			1.82	75	63	64	69		
			92	154	190	170	62	74	82	1.5	4							
			102	180	176	144	97	85	84	2.0	3							
G.H.	44,W,M	8	87	250	218	49						0.83	74	66	69	79		Convulsed at 2nd hour of initial O.G.T.T.
			78	156	130	110	51	57		1.5	6							
R.K.	29,W,M	8	85	176	219	121	40	85	79			1.73						Convulsed shortly after 5th hour of follow-up O.G.T.T.
			70	161	199	195	140	48	52	0.5	3							
G.D.	38,W,M	6	85	155	162	122	44	71				0.82	101	100	96	76	Yes	
			66	122	136	93	71	66	74	1.0	4							
W.B.	50,W,M	6	90	158	282	162	75	54	64			0.58	102	92	80	77		
			86	125	182	194	138	109	43	1.0	2							
			81	164	171	168	93	68	60	2.0	4							
E.V.	57,W,F	5	84	182	167	138	128	40	64	0.5		0.81	95	68	63	63		Not available for follow-up O.G.T.T.
B.S.	29,W,F	4	97	164	178	116	84	65	74				90	83	77	80	Yes	
			73	136	137	130	90	52	92	0.5	3							
M.C.	38,W,F	2	77	197	208	99	94	48	74	1.5	2		78	72	70	59		Not available for follow-up O.G.T.T.
D.C.	46,W,F	2	69	145	162	159	93	58	45			1.15	77	70	59	49		
			93	130	194	175	134	30	45	1.5	2							
A.A.	58,W,M	2	90	139	162	169	68	55	64			0.97	80	76	63	63	Yes	
			103	143	173	172	144	106	79	2.25	2							
E.H.	47,W,F	2	105	184	244	142	64	55	77	1.5			79	64	65	67		Not available for follow-up evaluation.
C.C.	72,W,F	2+	85	160	142	123	63	40		1.0		1.14	86	77	69	60		Changed residence after 2 months on therapy. Not available for follow-up.
D.B.	52,W,M	1	95	173	223	152	112	57	58	1.5								
M.D.	39,W,F		83	159	206	141	115	56	80	1.5		1.4						Referred for work-up. Therapy with tolbutamide recommended.
W.B.	44,W,M	0	75	170	195	162	35			1.5	0	1.82					Yes	Voluntarily discontinued therapy soon after initiation.

OGTT = Oral Glucose Tolerance Test
IVGTT = Intravenous Glucose Tolerance Test
TRT = Intravenous Tolbutamide Responsiveness Test
F.H. of D.M. = Family History of Diabetes Mellitus

of 0.8 or less reflects a definite impairment of glucose tolerance.

c. **Intravenous tolbutamide responsiveness test (T.R.T.).** After two fasting blood specimens were drawn, one gram of sodium tolbutamide dissolved in 20 ml. of sterile water was given intravenously over a 2 minute period. Blood specimens were then obtained 20, 30, 45, and 60 minutes after the injection was completed. The criteria for interpretation were those of Unger and Madison[15] and Kaplan[16] which correspond closely to our own values. A decrease of blood sugar to 80% or less of the average fasting value in the 20 minute sample and 77% or below in the 30 minute sample were considered satisfactory responses.

Prior to these examinations, all subjects had eaten diets high in carbohydrate for 1-3 days. In most instances, an evening dietary supplement of 100 grams of glucose was provided one or more days before testing. The procedures were initiated between 8:00 and 9:00 A.M. following an overnight fast. Only minimal physical activity was allowed, but smoking was not prohibited. In most instances, blood was drawn via an indwelling number 20 needle which was kept patent with periodic small injections of a dilute heparin solution. Blood glucose estimations were done on all specimens utilizing an Auto Analyzer (Technicon).

Duration of treatment ranged from 1 to 19 months with doses of tolbutamide ranging from 0.5 to 2.25 gms. per day (Table I). Patients were instructed to take 0.5 gm. tablets of tolbutamide one half hour before a meal. In most instances, a total of 1.5 gms. per day was prescribed. However, several patients either decreased the dose voluntarily or were instructed to do so by their referring physician.

RESULTS

All 21 patients had clinical episodes characteristic of hypoglycemia. These varied in frequency from several times per day, to once every 4-6 months, but in the majority of patients, attacks occurred more often than once weekly. The hypoglycemic reactions varied in severity as well. In general, they were not incapacitating. However, in two patients (W. B. and G. S.) the reactions were severe enough to abruptly interrupt routine activity. One patient (W. K.) experienced convulsive seizures 3-4 hours post-prandially. Neurologic evaluation, including a spinal fluid examination and electro-encephalogram revealed no abnormalities. Another patient (G. H.) had a grand mal seizure at the second hour of his intial O.G.T.T. when his blood sugar had fallen from 218 to 49 mg.%.

In contrast, none of the group had the more usual symptoms of diabetes such as weight loss, excessive appetite, thirst, or polyuria, nor was a history of ketosis elicited. Two patients (H. L. and D. C.) did complain of fatigue but it is of interest that this manifestation was most marked 3-4 hours post-prandially and was evident during the later phases of the O.G.T.T. when the blood sugar level was low. J. G. is the only patient who presented with a problem that could be construed as a complication of diabetes. He had a small ulcer above the right medial malleolus which healed promptly following the institution of therapy. Glycosuria on admission was noted in 3 and a family history of diabetes was obtained in 6 of the 21 patients. Other stigmata suggestive of diabetes including glycosuria during pregnancy (1 to 6), large birth weight (>9 lbs.) of children (2 of 6), and large birth weight of the patients themselves (2 of 12).

Frank obesity was evident in only 2 of our patients (W. D. and B. S.) who were 20 to 60 lbs. overweight at the start of therapy. There was no clinical or laboratory evidence of liver disease in any member of the series nor were there any findings suggestive of pituitary, adrenal or thyroid dysfunction. Islet cell tumor was never a serious consideration in any patient. Furthermore, of the 6 patients in whom the T.R.T. was performed, none showed the hyperresponsiveness

reported by Fajans et al.[17] characteristic of patients with insulinomas.

As recorded in Table I and Fig. 1, the O.G.T.T. was interpreted as showing borderline or clearly defined impairment in all 21 patients. Like Seltzer, Fajans and Conn[1], we have found the fasting blood sugar to be normal in the great majority of our patients. The 1 hour value was 160 mg.% or more in 86% of the group and the same proportion of patients had a 2 hour value of 110 mg.% or above. The mean 1 hour and 2 hour blood glucose levels were 193 and 135 mg.% respectively. A fall to below the fasting level, between the 3rd and 5th hour, was noted in all patients. The lowest values ranged between 24 and 65 mg.% with a mean of 49 mg.%.

Since the abnormality in oral glucose tolerance was borderline or mild in most instances, the I.V.G.T.T. and the T.R.T. were performed in an effort to clarify the diagnosis. The I.V.G.T.T. was performed in 18 patients; 10 of these showed clear-cut impairment of glucose disappearance. The T.R.T. was performed in 16 of the 21 patients. A delayed and diminished responsiveness was noted in 62%, and a borderline response in an additional 25%.

Seventeen of the 21 patients were available for clinical appraisal of therapy. In 12 of these 17 patients, a decrease in both number and intensity of the hypoglycemic reactions was noted. Of the remaining 5 patients, 2 (R. K. and E. V.) have shown no improvement. However, both had been following inadequate dosage schedules.

In the remaining 3 of our 17 patients, evaluation has been difficult. All 3 have shown a clinical response; however, one subject (M. H.) is being treated concomitantly with a tranquilizing drug and the other 2 subjects (W. D. and B. S.) have lost 20 and 30 lbs. since the therapeutic program began.

The O.G.T.T. was selected as an objective measure of the effect of tolbuta-

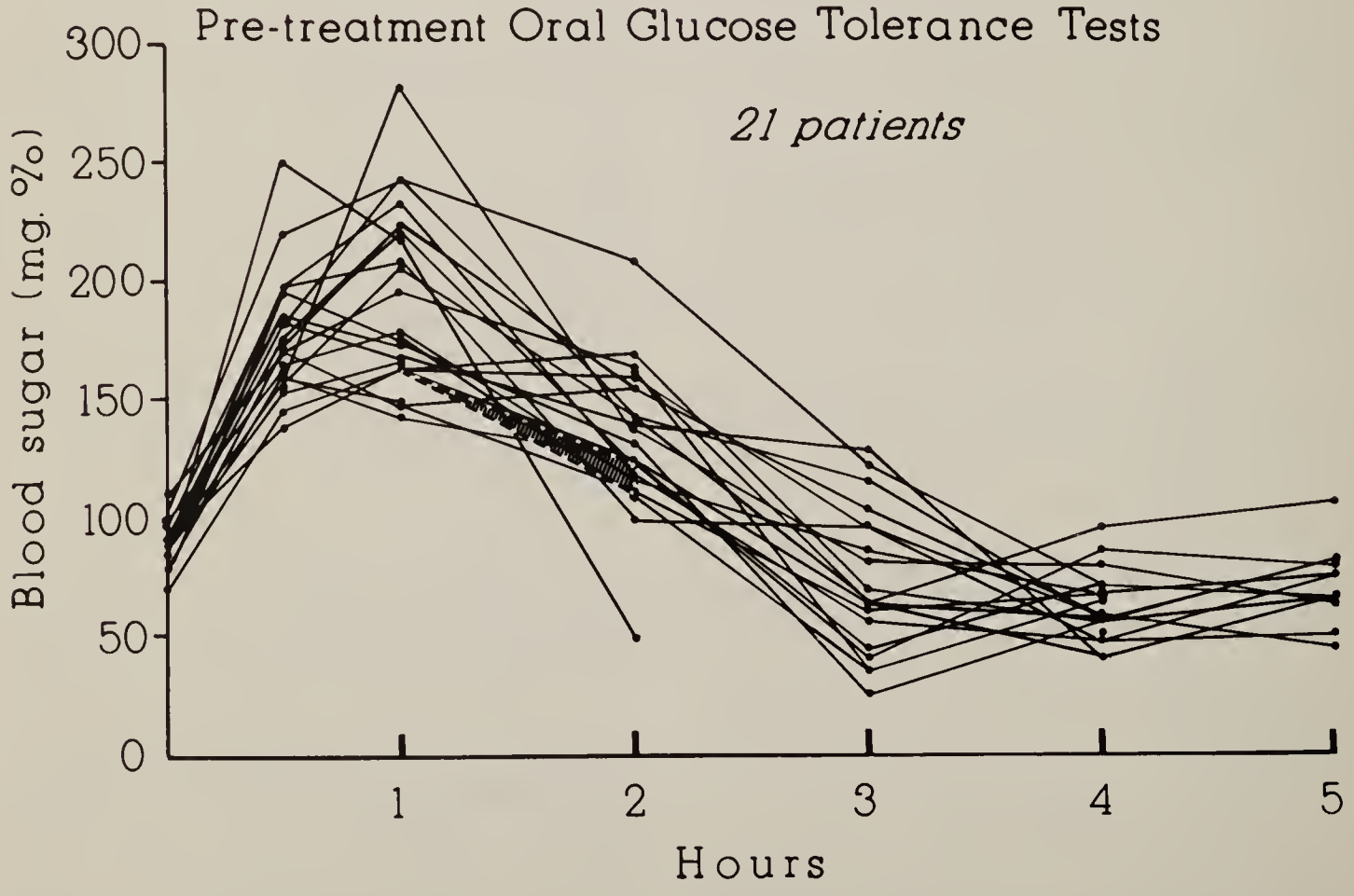

Fig. 1—Pre-treatment oral glucose tolerance curves of 21 patients.

mide therapy since of the 3 parameters used, this procedure most closely simulates the clinical setting of the study. In 14 patients, O.G.T.T.'s were carried out following therapy from 2 to 19 months duration. Good responses, as illustrated in Fig. 2 were observed in 5 patients. In the 2 examples shown (W. D. and M. H.) tolbutamide therapy was associated with a reduction in both early hyperglycemia and late hypoglycemia, i.e., normalization of the curve.

An equivocal response was observed in an additional 4 patients as demonstrated in Fig. 3. Patients G. H. (Fig. 3A) and B. S. showed a partial response in that the hyperglycemia was considerably reduced while the later hypoglycemia remained relatively unaltered. Conversely, in patients A. A. (Fig. 3B) and N. S., the early hyperglycemia remained unaffected while the hypoglycemia was ameliorated.

A poor objective response was noted in the remaining 5 patients as exemplified by patients R. K. and D. C. in Fig. 4. It should be recalled that 2 patients (R. K. and G. S.) of this group received only 0.5 gms tolbutamide per day.

DISCUSSION

Clinical and biochemical evidence of hypoglycemia associated with the diabetic state is not an infrequent finding. Seltzer, Fajans and Conn[1] state that its incidence is exceeded only by that of functional hyperinsulinism but our own preliminary experience suggests that it may be the commonest form of hypoglycemia. Furthermore, we wonder

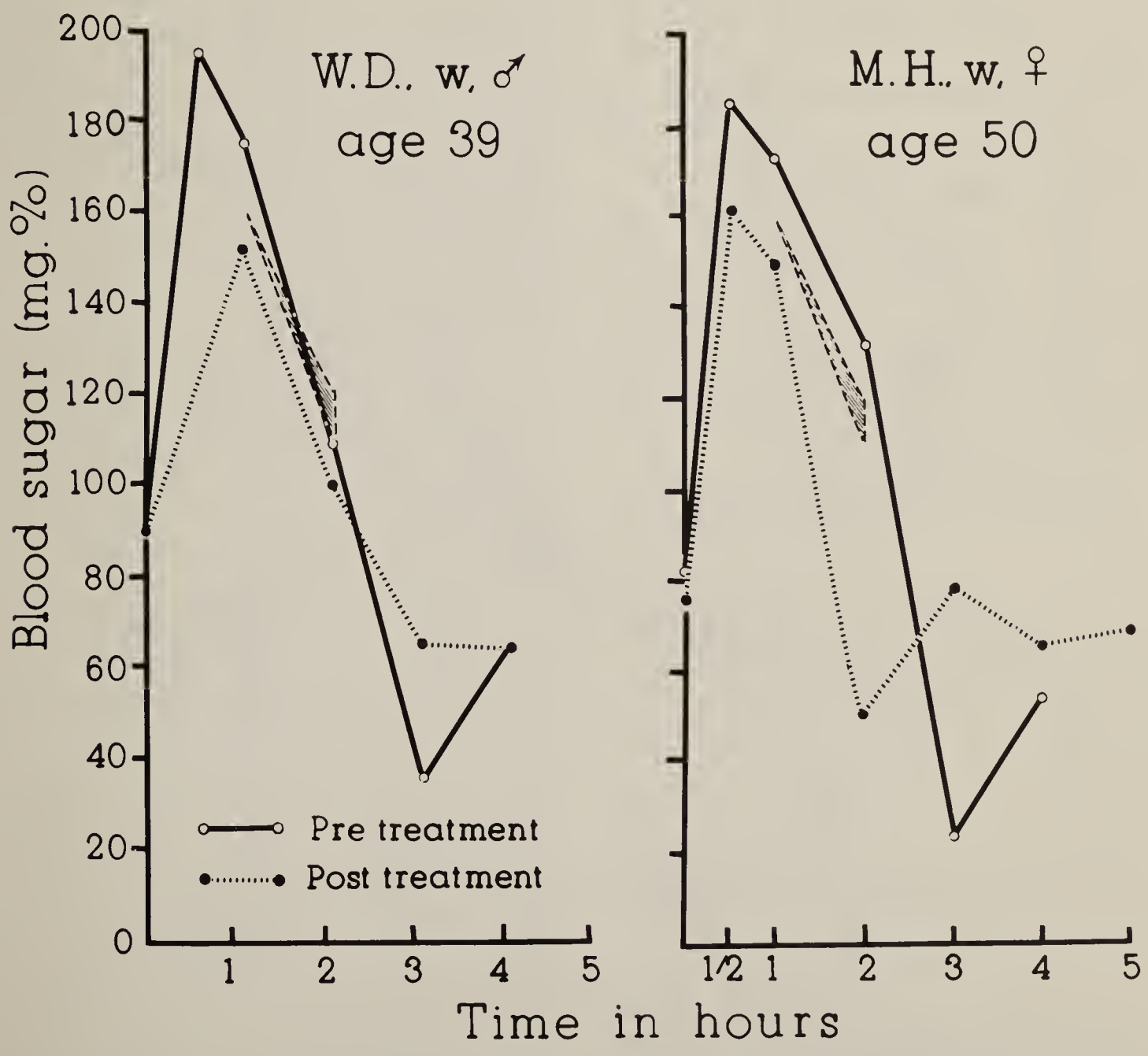

Fig. 2—Two examples of pre- and post-treatment oral glucose tolerance curves illustrating good response to therapy.

whether many patients with "functional hyperinsulinism" may, in fact, be pre-diabetics.

The diagnosis of spontaneous diabetic hypoglycemia usually requires only the performance of a 5 hour O.G.T.T. However, occasionally as in patients W. D., R. W., G. D., B. S., and C. C., the hyperglycemic phase may show only borderline abnormalities. In these individuals, the I.V.G.T.T. and the T.R.T. may be helpful in supporting the diagnosis.

It seems paradoxical to treat hypoglycemia with a hypoglycemic agent; however, the rationale for the use of tolbutamide in our patients is to reduce or prevent the initial hyperglycemic phase which we feel is related to the later hypoglycemic symptoms. Extrapolating from

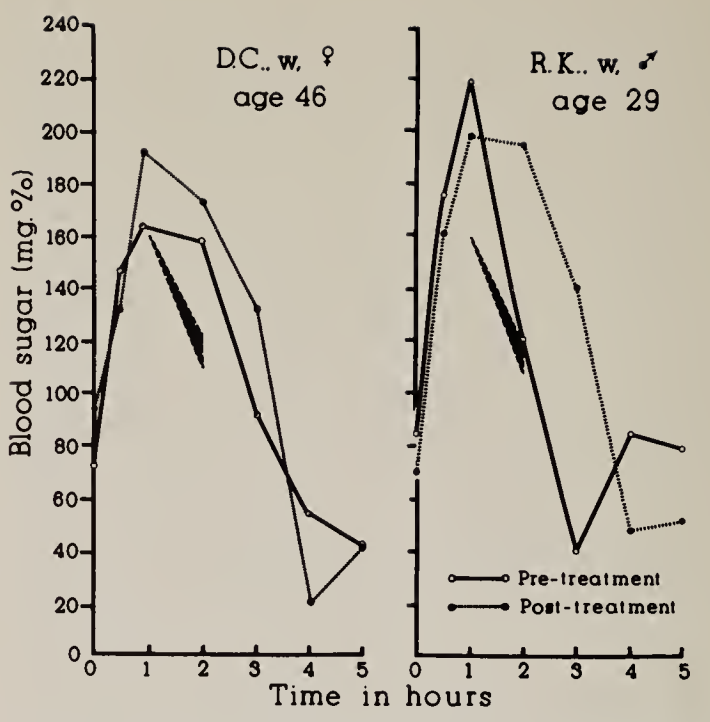

Fig. 4—Pre- and post-treatment oral glucose tolerance curves demonstrating no objective response to therapy.

the studies of Yalow and Berson[9] of plasma insulin levels in maturity-onset diabetic subjects, the use of tolbutamide might conceivably reduce the late, significant rise in plasma insulin levels of these patients by decreasing the initial hyperglycemic peak. In 5 of the 14 follow-up patients, in whom treatment was objectively evaluated, such an explanation seems reasonable.

Four of our patients improved clinically despite an equivocal response as measured by the O.G.T.T. It is reasonable to assume that the improvement in symptoms may be explained by the decrease in the rate of fall of the blood sugar level. Indeed, it is possible that elimination of wide swings in blood glucose levels may be efficacious in other disorders. A case in point is provided by a patient, not included in this study, who had a post-gastrectomy "dumping syndrome" with severe symptoms which were clearly associated with post-prandial hypoglycemia. An O.G.T.T. revealed an initial hyperglycemic peak followed by an impressive fall from 198 mg.% at the 2nd hour to 45 mg.% at the 3rd hour. It became of interest to us to determine whether the hypoglycemic symptoms experienced by this patient could be aleviated. The patient was treated with tolbutamide and his clinical re-

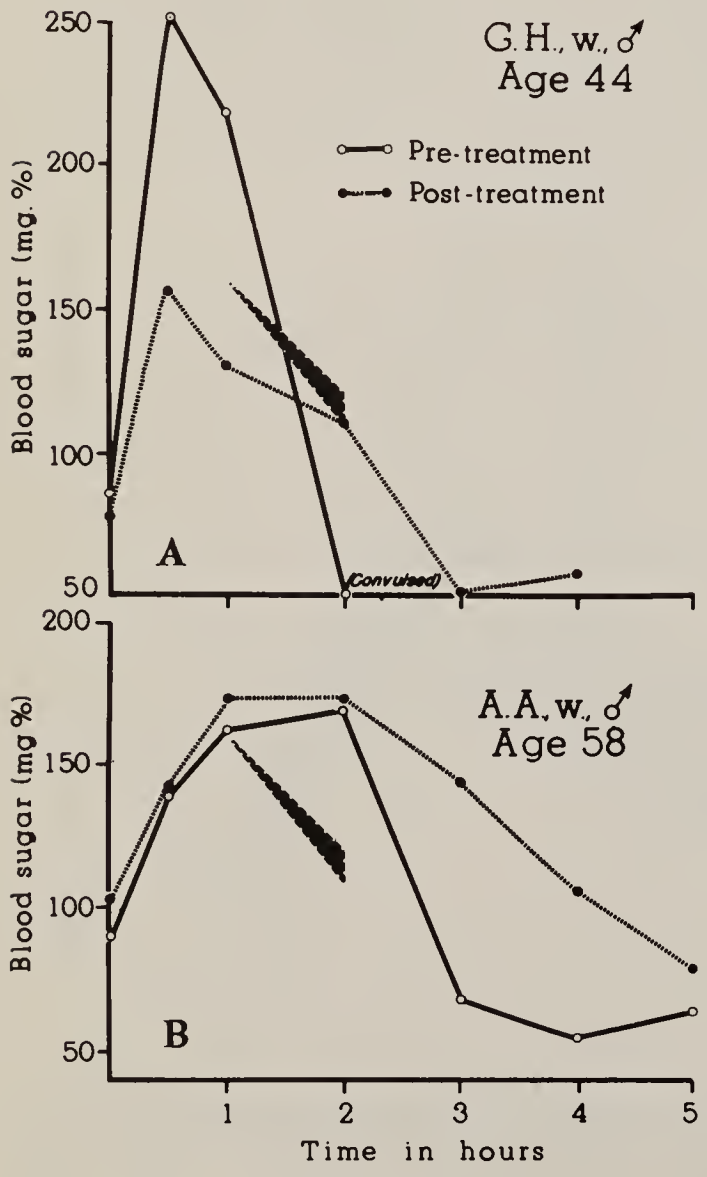

Fig. 3—Pre- and post-treatment oral glucose tolerance curves demonstrating partial response to therapy. Patient G.H. illustrates reduction of hyperglycemia only. Patient A.A. illustrates disappearance of hypoglycemic level.

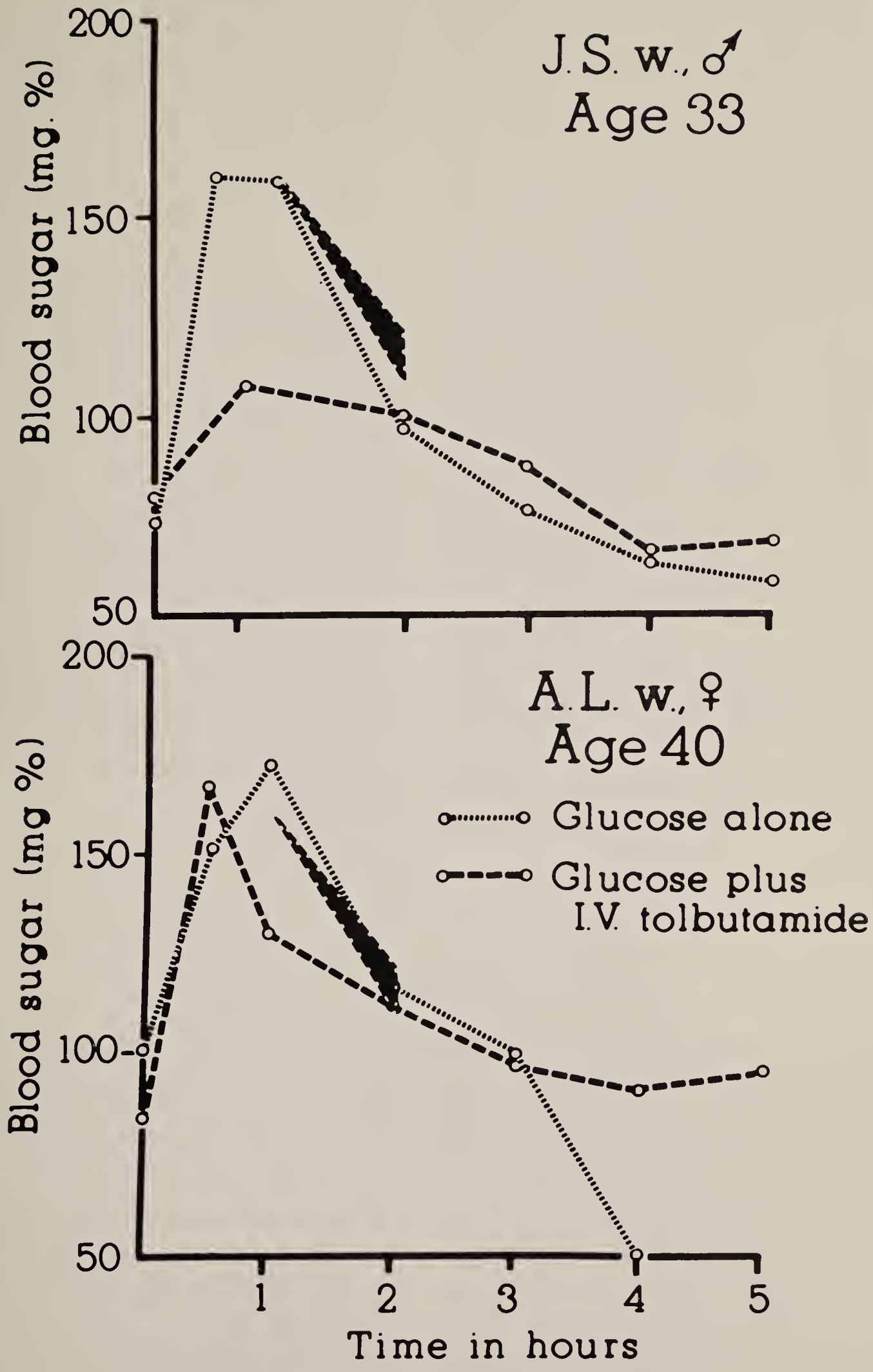

Fig. 5—Examples of oral glucose tolerance curves obtained when sodium tolbutamide, 1 gm. I.V., was given at the time of glucose ingestion. J. S. is a normal subject. Patient A.L. has prediabetic hypoglycemia.

sponse was quite dramatic. When the O.G.T.T. was repeated, it was found that although the later hypoglycemia persisted, the initial hyperglycemia had been eliminated. Here too, the decrease in the magnitude of fall of blood sugar concentration may have been contributory to this patient's clinical improvement.

We have been somewhat disconcerted to find that of the 5 patients who showed no acceptable evidence of objective response, clinical improvement occurred in 4. There is no ready explanation for this discrepancy. Indeed, all the manifestations of clinical improvement observed in this study may be illusory; "double blind" techniques were not employed. Nevertheless, since symptomatic and objective evidences of improvement did occur concurrently in the majority of our patients, the attribution of all our findings to a "placebo effect" seems unwarranted.

Recently, the study has been broadened to observe the effect on the O.G.T.T. when intravenous sodium tolbutamide and the oral glucose load are given simultaneously to patients similar to those reported here. Again, too few data are as yet available for definitive conclusions, but it appears that the same type of response, seen in the more protracted studies may be obtained. A good response is charted in Fig. 5 (patient A.L.) along with the same results of the same procedure carried out in a normal subject for comparison (patient J. S.). A reduction in both the hyperglycemic and hypoglycemic phases is noted. We are hopeful that this procedure will enable us to predict long term response to therapy in a fashion similar to the technique employed by Camerini-Davalos, Root and Marble[18] and Marble[19], in diabetics without apparent hypoglycemia.

Treatment of the early diabetic state associated with hypoglycemia may be important for other reasons. Fajans and Conn[20] recently reported the use of tolbutamide in the treatment of asymptomatic juvenile diabetics. Their results have shown that carbohydrate tolerance improved or became normal in 13 of 14 patients during treatment with tolbutamide. It is hoped that continuation of this treatment may prevent the onset of frank diabetes mellitus not only in asymptomatic juvenile diabetics, but also in patients with mild early diabetes or prediabetes associated with hypoglycemia.

SUMMARY

The use of tolbutamide for the treatment of symptomatic prediabetic hypoglycemia has been investigated in 21 patients. The diagnosis of hypoglycemia secondary to mild or prediabetes was based on distinctive clinical episodes of post-prandial hypoglycemia and an abnormality of the oral glucose tolerance test showing an initial hyperglycemic phase with a later hypoglycemic level. The intravenous glucose tolerance test and the T.R.T. were employed in borderline cases to establish a diagnosis of diabetes.

The rationale for the use of tolbutamide was to reduce or prevent the initial rise in blood sugar which we feel is related to the later hypoglycemic symptoms.

Of 17 patients available for follow-up, 12 have shown impressive clinical improvement, 3 cannot be adequately evaluated, and 2 showed no response to therapy. In 14 subjects in whom the oral glucose tolerance test was repeated following therapy for as long as 2 to 19 months, normalization of the curve was noted in 5, partial response in 4, and no change in 5. Four of the latter have shown clinical improvement.

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FLUORESCENCE MICROSCOPY: Some Clinical and Research Applications

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INTRODUCTION

Microbiology and immunology have long suffered from the lack of a procedure which combines rapidity and specificity of identification. Trying to remedy this lack, Coons showed in 1942 that antibody globulin would combine with compounds related to fluorescein thus putting a visible "label" on immunoproteins. Since that time, and particularly in the past ten years, fluorescein tagged antibodies have found ever-increasing application in all of the fields where antigen-antibody reactions are studied.

As we have become familiar with the use of the ultraviolet microscope in these studies we have found other fluorescent dyes or fluorochromes which, though not used to label antibody protein, have been of great value because of their cytochemical properties. One such substance is acridine orange which enables us to distinguish DNA from RNA rapidly and simply.

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These, then, are two relatively new techniques with which many physicians are unfamiliar but which are coming into ever-increasing use in both the clinical and basic sciences. This communication briefly describes the technical procedures invloved and enumerates some important applications to which they may be put.

TECHNICAL PROCEDURES

1. Fluorescent labelling of antibodies: Any serum can be used, whether a specimen collected from a patient or an antiserum prepared in a test animal. The specific details of preparation are described in a recent paper from this laboratory[1], but in general terms the first step is the separation of the globulin fraction by salting out. This fraction, redissolved, is incubated at 4° C. with fluorescein isothiocyanate (FITC) during which time the FITC conjugates with the gamma globulin. Unconjugated FITC and FITC attached to non-gamma globulins are removed by column fractionation leaving a specifically labelled

gamma globulin fraction. This is the substance used in fluorescent antibody staining.

2. Staining of preparations: Tissue sections made by frozen section or cell cultures grown on coverslips and fixed by air drying plus acetone are washed in pH 7.2 phosphate-saline buffer, incubated at 37° C. with FITC tagged globulin for an hour, rinsed three times in the same buffer, mounted in a non-fluorescing medium[2] and studied in the ultraviolet microscope.

3. Acridine orange stain: Infected and uninfected cell cultures grown on coverslips are fixed in acid alcohol and stained with 0.01% acridine orange at pH 3.9 by the method of Starr, et. al.[3]. When such preparations are studied with the ultraviolet microscope ribonucleic acid (RNA) fluoresces orange-red and deoxyribonucleic acid (DNA) fluoresces yellow-green. If, however, double-stranded RNA is present it will stain yellow-green also. For this reason it is wise to confirm the identity of the nucleic acids present by treatment with DNA-ase or RNA-ase[4].

4. Ultraviolet microscope: In our laboratory a Zeiss Model GFL fluorescent microscope and a Mercury vapor lamp (Osram HBO-200) as the exciting source were employed. The exciting filters were UG-2 and BF12 with a Schott KG1 heat absorbing filter. Barrier filters were "New Schott Designation" 50 and 41.

APPLICATIONS

1. Diagnosis and Epidemiological Survey: Fluorescein tagged antibodies can under certain circumstances yield a rapid diagnosis. If tissues or exfoliated cells are readily available the antibodies can be reacted directly with the specimen and such a technique is now used routinely for the identification of rabies virus in brain tissue of suspect animals. Fluorescent antibody staining of exfoliated nasal cells was used in a survey of an influenza epidemic[5] and these authors were able to arrive at a positive diagnosis of influenza in a matter of minutes in this study. Similarly Page and Stulberg[6] were able to identify specific enterovirus infection by immunofluorescent study of stool, spinal fluid, or both. The epidemiological value of immunofluorescence is discussed in greater detail in a recent paper by Schaeffer, Orsi and Widelock[7].

In a similar fashion a definite diagnosis can be rendered rapidly by the virus diagnostic laboratory if a specific fluorescent antibody can be shown to react with an infected cell culture.

The diagnostic uses of immunofluorescence are not confined to virology but are applicable to other types of infectious disease as well. The fluorescent treponemal antigen test (a reliable procedure in the diagnosis of syphilis) utilizes fluorescein tagging, and a wide variety of bacterial infections can be diagnosed rapidly by reaction of specific antisera with exudates or infected tissues. Unfortunately, with the exception of pathogenic *E. coli*, the enteric bacterial infections have not proved amenable to diagnosis by this technique because of too many cross reactions among the members of the Salmonella and Shigella groups.

In a somewhat different field of endeavor, the detection of antinuclear antibodies has been found valuable in the diagnosis of systemic lupus erythematosus and other diseases of connective tissue. In this procedure attachment of antibodies to nuclei is demonstrated by the addition of FITC tagged antibodies against human gamma globulin.

The use of acridine orange is not so important in microbiological diagnosis but it has found widespread diagnostic application in exfoliative cytology[8]. It is of some limited value in the virus diagnostic laboratory since by revealing the type of nucleic acid in the infecting virus it provides a first step in identifying an unknown isolate.

2. Research: Both immunofluorescence and acridine orange staining have proved valuable in investigations of *in vivo* and *in vitro* virus infection. The buildup of viral nucleic acid in the infected cell can be followed accurately with acridine orange (Figures 1 and 2) and the devel-

opment of antigenic virus is easily detected by immunofluorescence (Figures 3-6). Much of our current knowledge of virus replication is based on such studies.

Just as fluorescein tagged antibodies enable us to follow the progress of infection in a cell culture, so also are they of value in the study of the pathogenesis of disease in the whole animal. Here they enable us to detect foci of virus multiplication in involved organs (Figure 7) or even infection of single cells (Figure 8).

The role of autoimmunity as a cause or perpetuating factor in many diseases of hitherto unknown etiology is currently under study in many laboratories. By preparing FITC tagged antibodies against human gamma globulin or other serum proteins and staining of sections of involved organs the cellular localization of the offending proteins is greatly facilitated.

DISCUSSION

A number of applications of fluorescent microscopy have been enumerated, and they show the various contributions which may be made by these techniques. Because of the interests of this laboratory emphasis has been placed on the infectious diseases but this should not detract from the major contributions which are being made through the widespread use of fluorescence microscopy in the study of non-infectious diseases as well. These techniques, which were unknown to us little more than a decade ago have become routine in many research laboratories and are being seen increasingly frequently in the clinical laboratory as well.

SUMMARY

The techniques of fluorescein tagging of antibodies and acridine orange staining are described briefly and some of their uses are discussed. These procedures, originating in the microbiology laboratory, are coming into ever increasing use in the diagnosis and study of both infectious and non-infectious disease.

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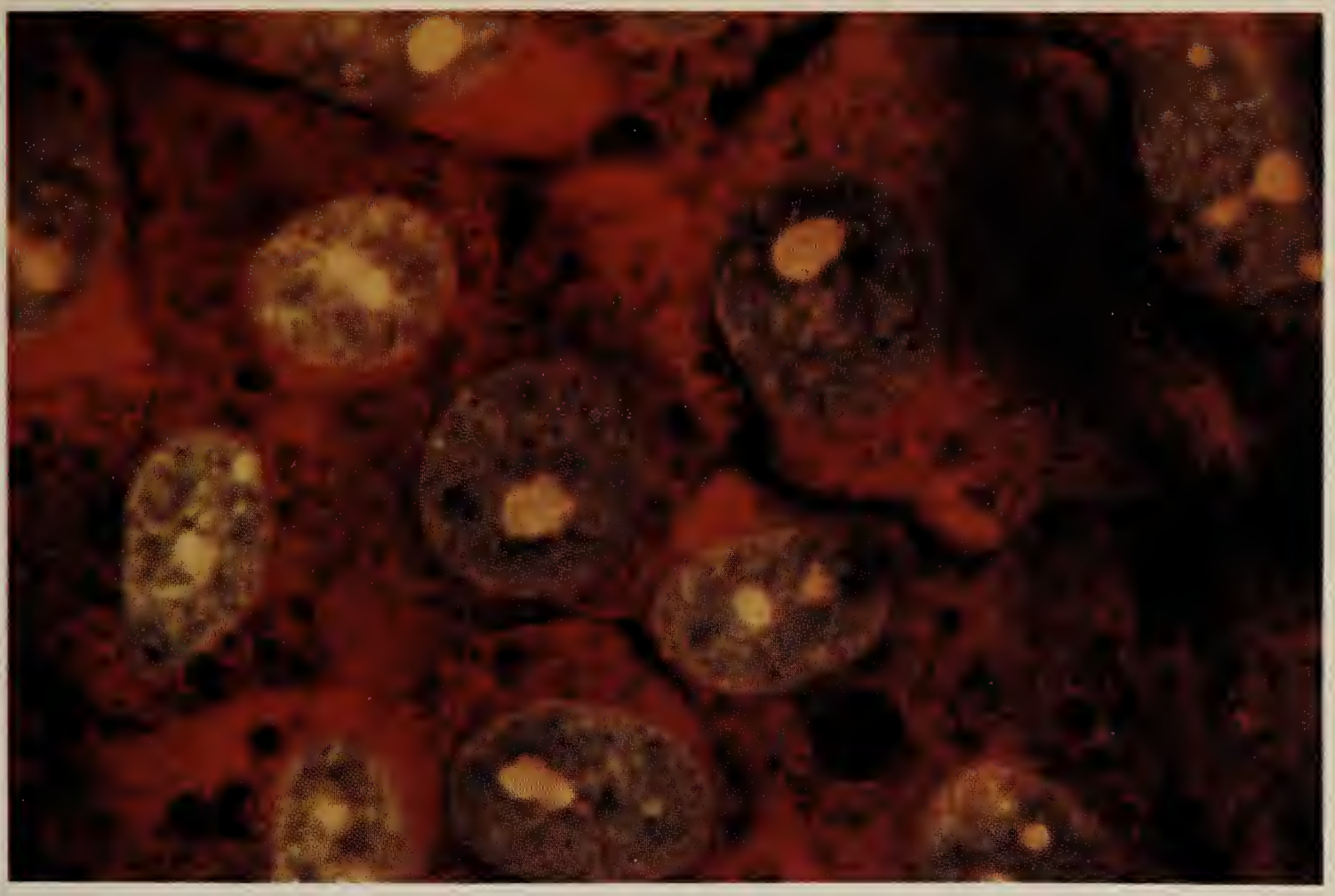

Fig. 1.—Normal HEp-2 cell culture stained with acridine orange. (x400 original magnification)

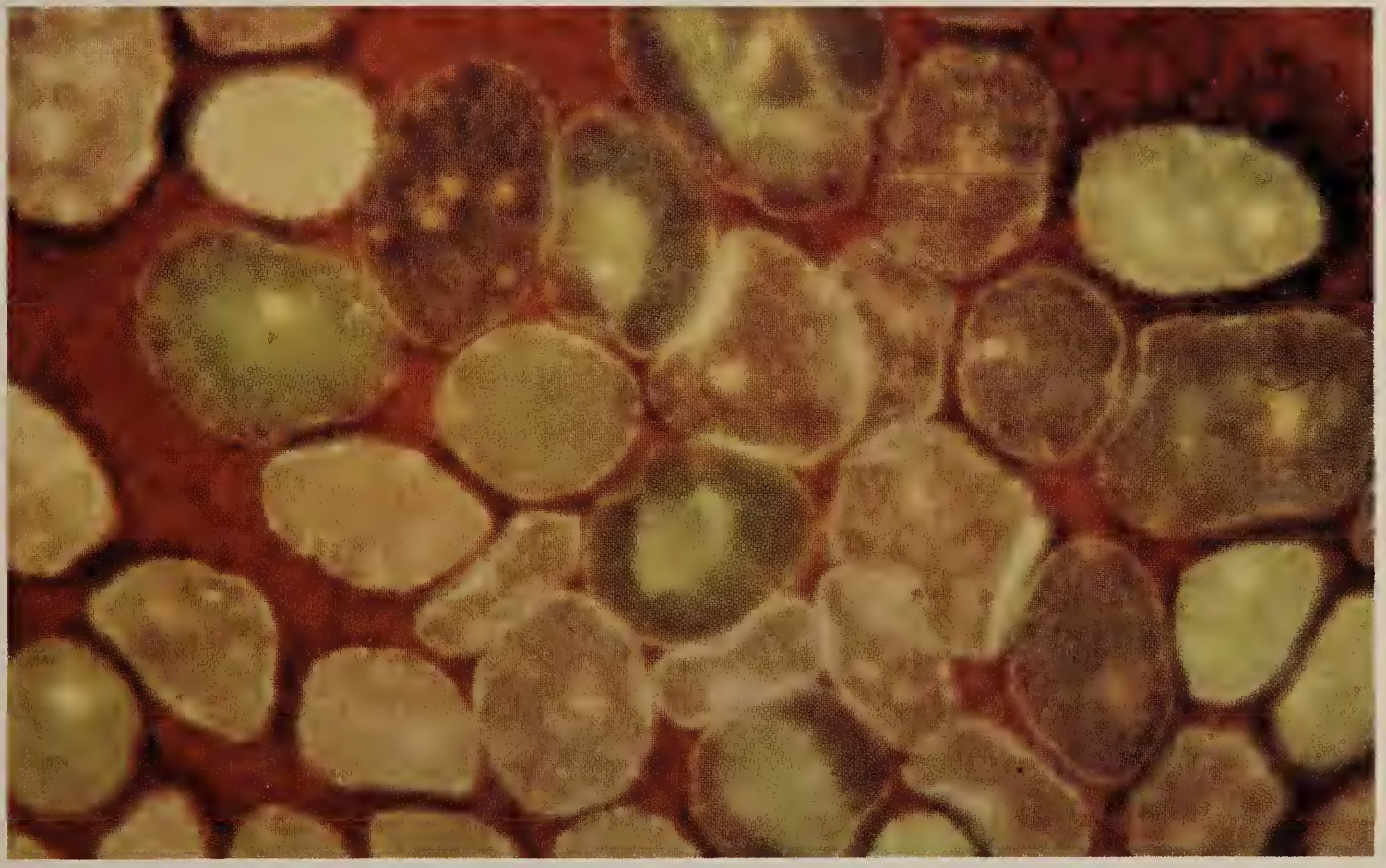

Fig. 2.—HEp-2 cell culture infected with adenovirus type 5, acridine orange stain. Note the diffuse green intranuclear fluorescence which is an early stage of the discrete intranuclear inclusion body. (x400 original magnification)

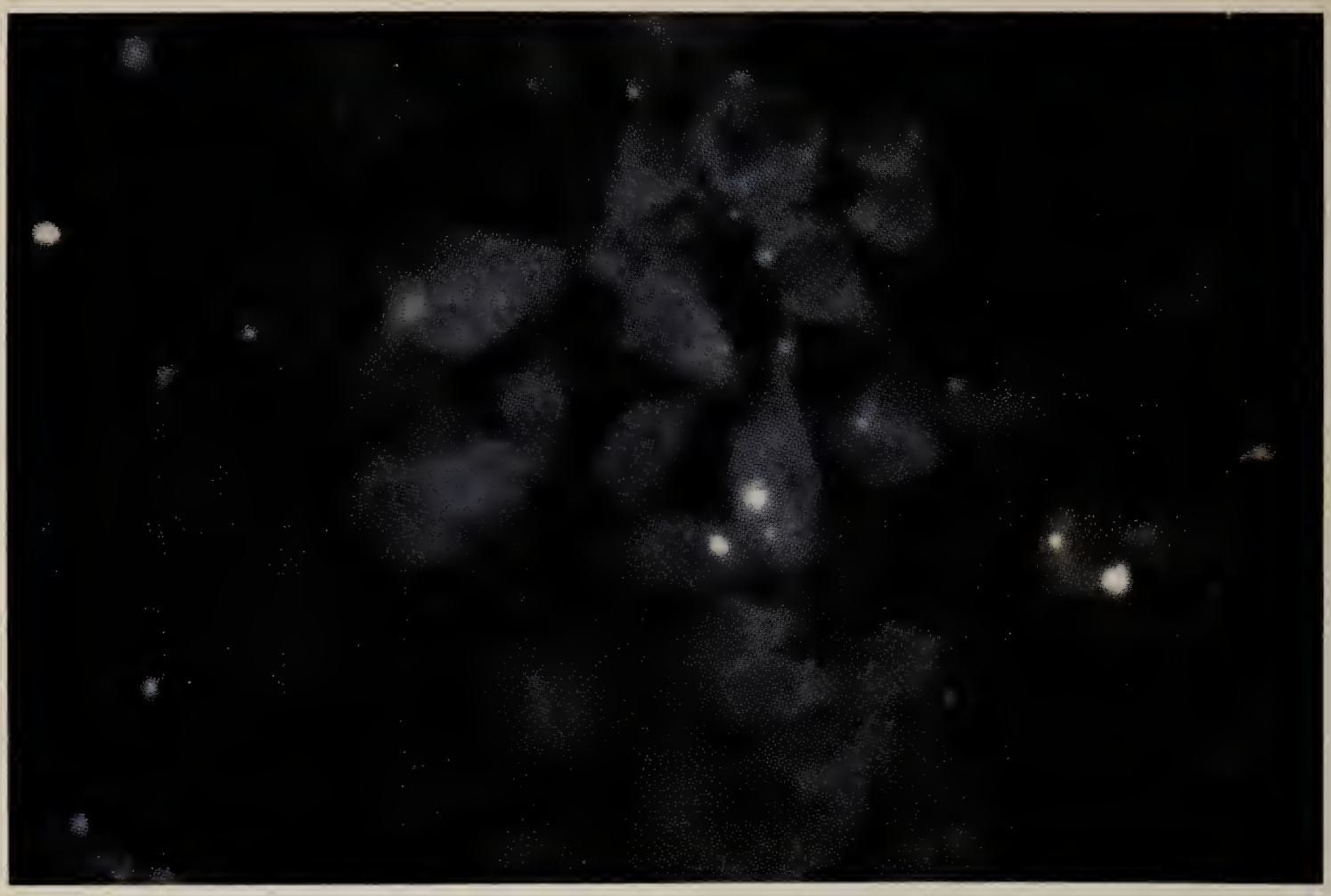

Fig. 3.—MCN cell culture, uninfected, used as control for fluorescent antibody stain. Note the faint bluish autofluorescence which is of no significance. (x100 original magnification)

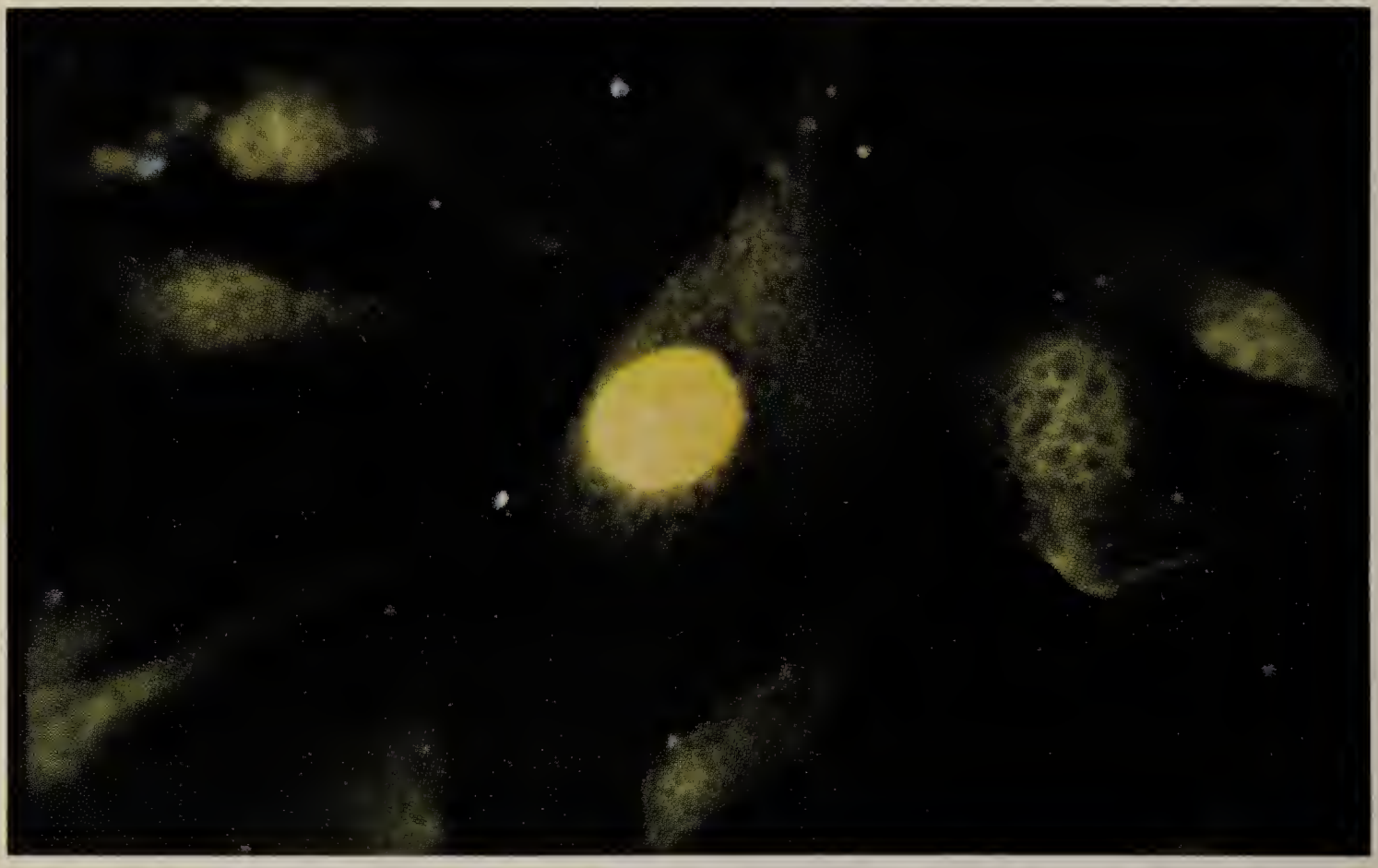

Fig. 4.—Nuclear fluorescence in an MCN cell infected with polyoma virus. (x400 original magnification)

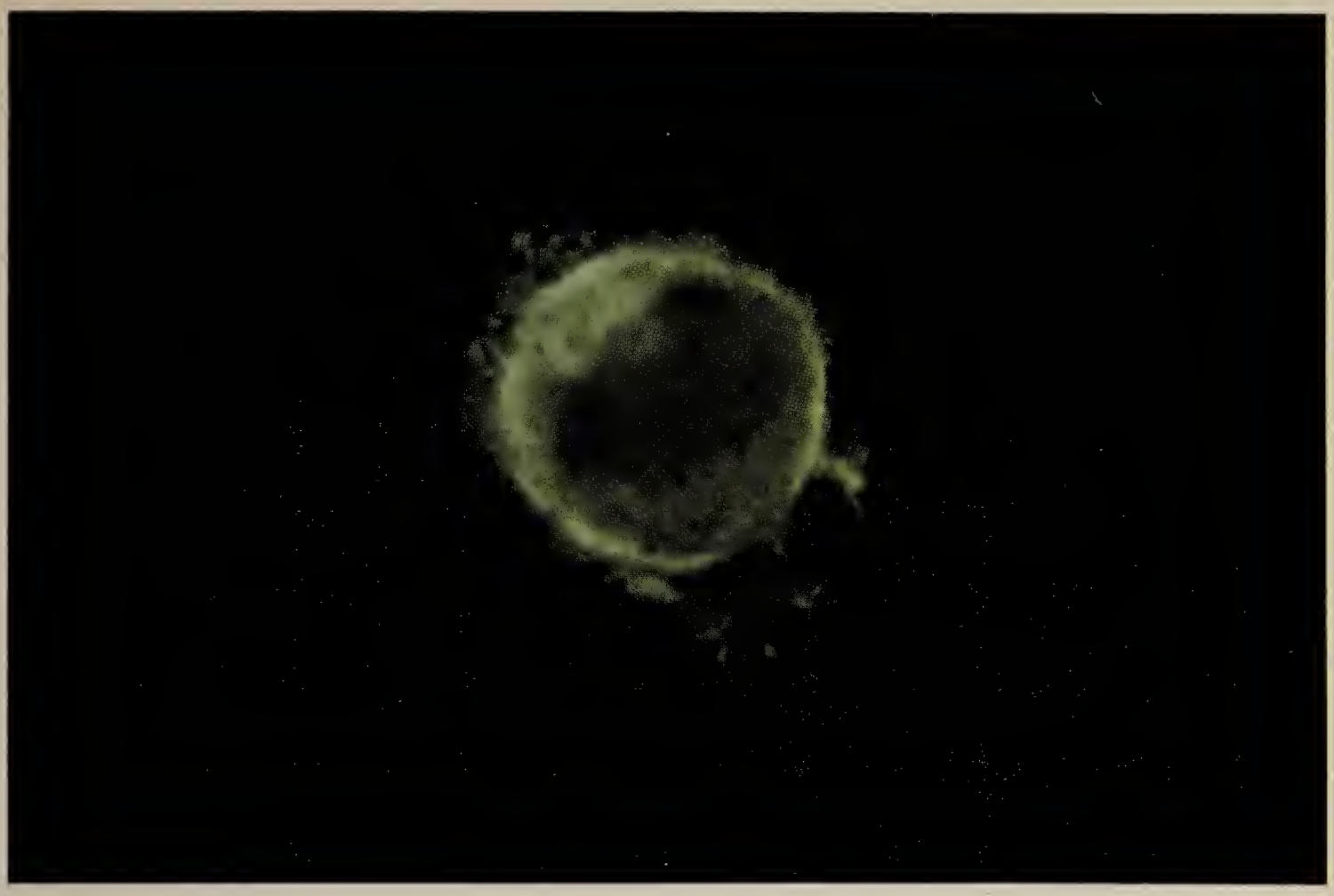

Fig. 5.—Cytoplasmic fluorescence in a HEp-2 cell infected with herpes simplex virus. (x400 original magnification)

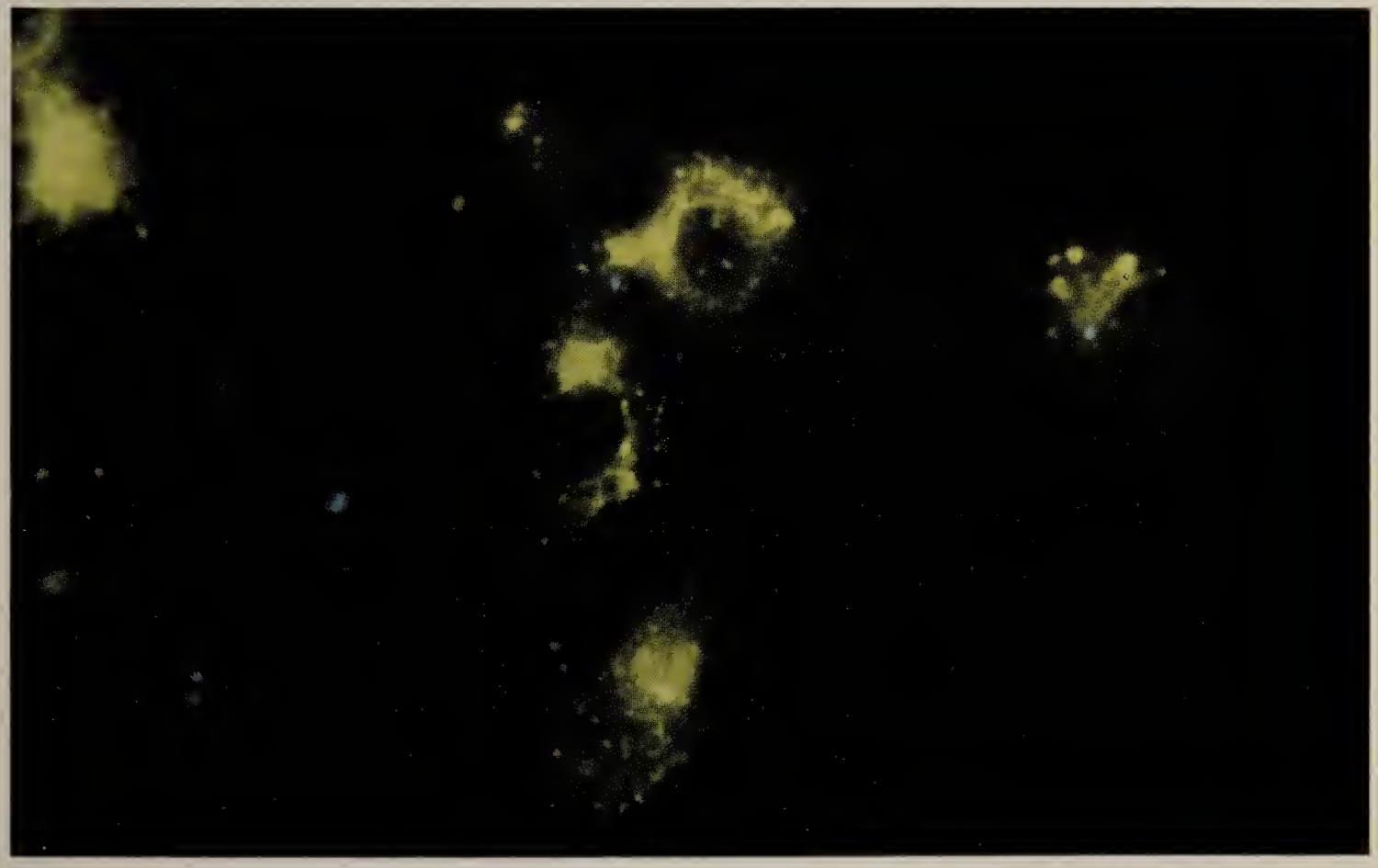

Fig. 6.—MCN cell culture infected with mumps virus. Note yellow-green fluorescence indicating presence of antigenic virus in cytoplasm. (x400 original magnification)

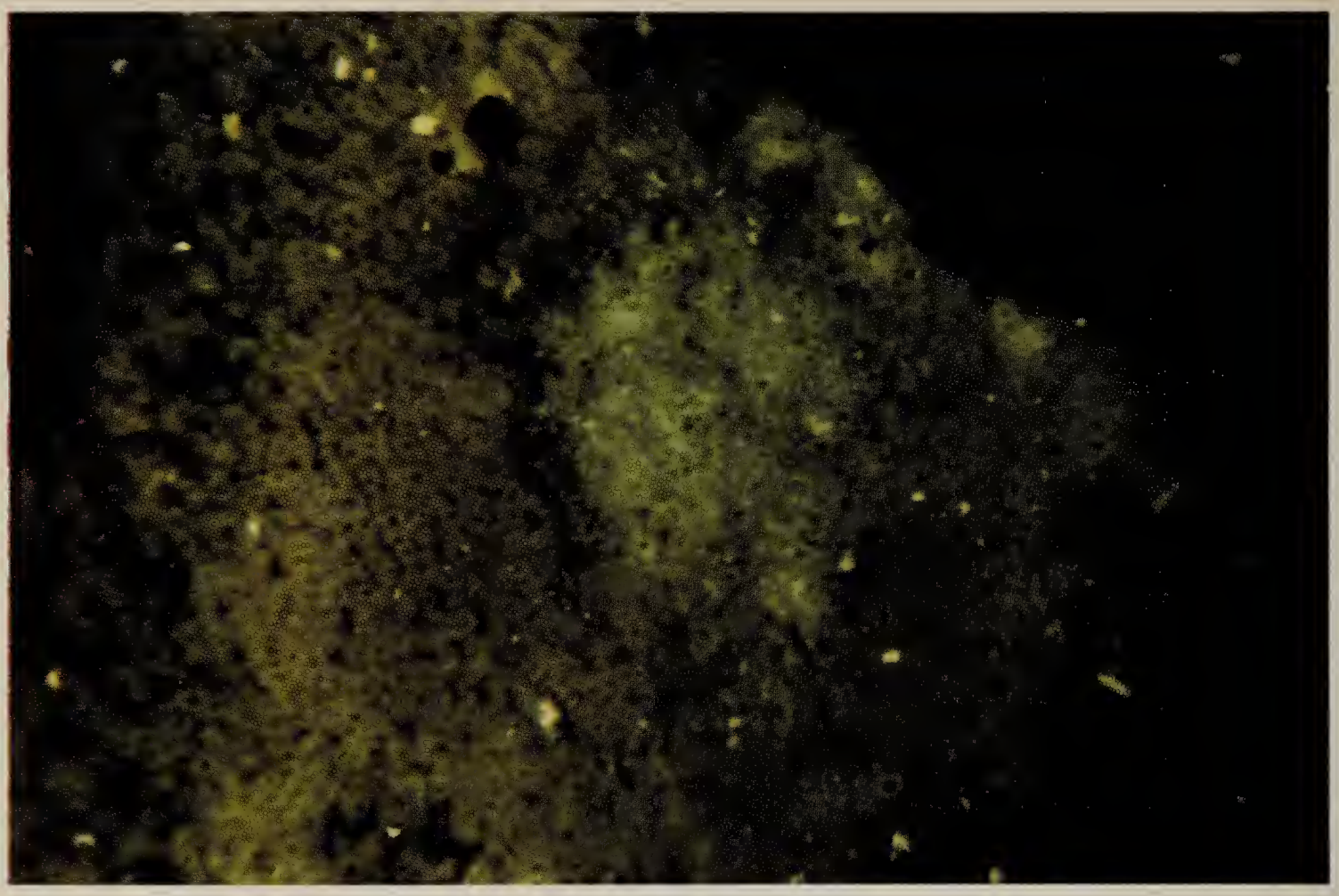

Fig. 7.—Area of fluorescence (bright yellow-green) in adrenal of a marmoset infected with herpes M virus. (x100 original magnification)

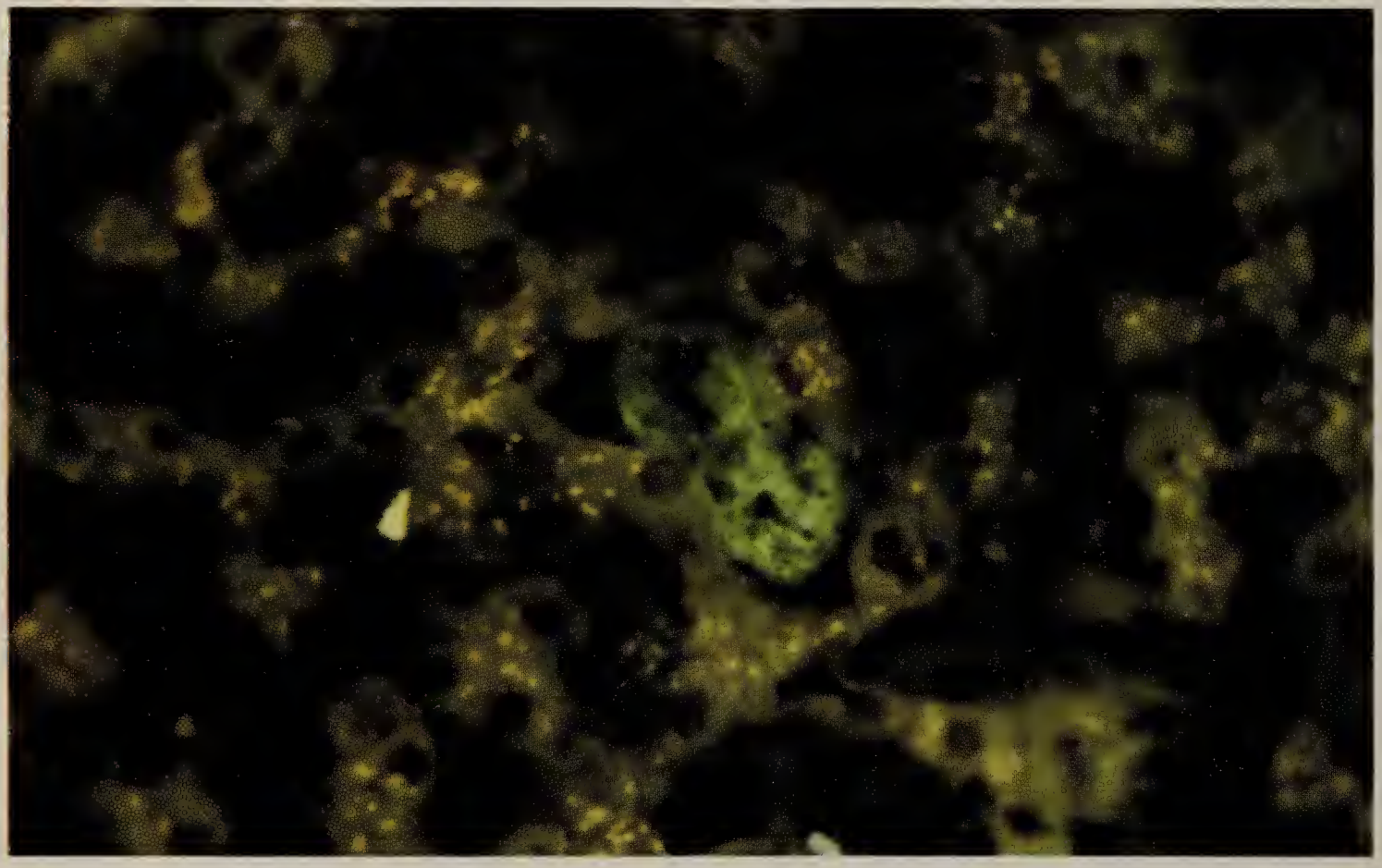

Fig. 8.—Fluorescence of a single cell, probably a Kupffer cell in the liver of a marmoset infected with herpes M virus. (x400 original magnification)

THE NEWER PROGESTERONES

ARTHUR H. KLAWANS, M.D.[1]

INTRODUCTION

Progestin, the corpus luteum hormone, has long been known to be important if not essential in providing the decidual bed for implantation of the ovum and maintenance of the pregnancy. It has been taught that inadequacies, destruction or removal of the corpus luteum of pregnancy result in abortion. Because of this, many corpus luteum extracts had been used in the treatment or prevention of abortion. As a result of the successful synthesis of a progesterone about ten years ago, the great era of clinical application of the synthetic progesterones began. We now have many such products in our drug armamentarium with many recommended uses.

PROGESTERONES

These products are used to replace or enhance the normal progestins in conditions where these are felt to be diminished or lacking. Their value is proved as a test for pregnancy, producing a pseudo-pregnancy decidua-like endometrium after several days of use. When they are discontinued the support of the endometrium is withdrawn and bleeding ensues. Thus, if the patient bleeds, she is not pregnant. If pregnant, the progesterones serve to enhance the decidua and provide a more solid implantation of the fertilized ovum. The latter action is the one that provides the rationale for the use of the progestational hormones in threatened and habitual abortions.

The progesterones also are felt to have some pituitary inhibiting action and thus suppress the production of follicle stimulating hormone and the development of ovulation. However, this action is not absolute. Estrogenic hormone produces a greater assurance of pituitary, and therefore ovulatory suppression.

When progesterone is used the more lush endometrium produced is decidua-like and will not slough to produce menstruation-like bleeding. This hormone also acts to reduce uterine muscular activity and contraction. (Table 1)

THE PROGESTERONE-ESTROGEN COMBINATIONS

The chief practical use of these products is in the area of contraception. The combined pituitary suppressing activity of both hormones assures the suppression of ovulation and thus, the prevention of pregnancy.

In the first half of the normal cycle the estrogenic hormone builds the endometrium (proliferative phase) and after ovulation the corpus luteum produces progesterone while the estrins diminish. Still, at the time of the onset of menstruation the normal combination of estrogen-progesterones provide the endometrial stroma for the fertilized ovum, if one exists. If a fertilized ovum does not exist the production of these hormones ceases, the endometrial support is withdrawn

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TABLE 1—THE PROGESTERONES

Proprietary Name	Manufacturer	Scientific Name	Range of Usual Recommended Daily Dose (mg)
Delalutin	Squibb	Hydroprogesterone caproate	125-250
Depo-Provera	Upjohn	Medroxyprogesterone acetate	50
Duphaston	Philips-Roxane	Dyhydrogesterone	10
Norlutate	Parke-Davis	Norethyndrone acetate	5
Provera	Upjohn	Medroxyprogesterone acetate	10

and menstruation ensues. Thus, the use of a drug which provides these hormones results in a "pseudo-pregnancy" endometrium and the withdrawal of the drug results in bleeding. (Table 2)

CLINICAL APPLICATION

One product has practically no advantage over another and except for the areas of contraception and pregnancy test, the value of these products in other clinical situations is equivocal. (Table 3)

Contraception

Because of the uncertainty of complete suppression of ovulation by the straight progesterones, the progesterone-estrogen combinations are safer and are preferred. The contraceptive quality of one product is the same as that of another. Since the lower dosages have proved to be as satisfactory as the higher ones, we should prescribe the former. All of these products are used in the same way. Starting on day five of the menstrual cycle (day one being the first day of menstrual bleeding) one tablet* is taken each day for 20 days. The tablet should be taken at the same time each day. In one to three days after stopping taking the tablets, menstrual

TABLE 2—ORAL PROGESTERONE-ESTROGEN COMBINATIONS

Proprietary Name	Manufacturer	Combinations	Range of Usual Recommended Daily Dose (mg.)
Duosterone	Roussel	Ethistrone Ethinyl Estradiol	50 0.05
Enovid	Searle	Norethyndrel Acetate Ethinyl Estradiol (Mestranol)	2.5, 5, 10 0.075, 0.15
Gestest	Squibb	Norethyndrone Acetate	2.5
Norlestrin	Parke-Davis	Norethyndrone Acetate Ethinyl Estradiol	2.5 0.05
Orthonovum	Ortho	Norethyndrone Acetate Ethinyl Estradiol	2 0.10
Pro-Duosterone	Roussel	Norethyndrone Acetate Ethinyl Estradiol	50 2
Norinyl	Syntex	Norethyndrone Acetate Ethinyl Estradiol	2 0.10
Provest	Upjohn	Medroxyprogesterone acetate Ethinyl Estradiol	10 0.05

*The tablet dose of the various agents corresponds to the usual recommended daily dose.

TABLE 3—CONTRACEPTIVES

Drug	Dosage Day 5 to 24
Enovid	2.5 mg.
Norlestrin	2.5 mg.
Orthonovum	2 mg.
Norinyl	2 mg.
Provest	10 mg.

bleeding should begin. On the fifth day of the bleeding the medication is restarted with repetition of the process cyclically. (Table 3)

At the outset, about ten days should elapse after the start of the regimen before the patient can be considered safe from pregnancy. In succeeding cycles, following the schedule set above, there should be complete safety at all times. It has been said that after stopping the use of these hormones fertility is increased.

At the present time it is considered safe to practice contraception by this method for four years. The question arises in the minds of many as to what will prolonged suppression of the pituitary and the ovary do to those organs or to the rest of the endocrine system. If a young married woman who is in her early 20's is started on this routine will she be able to practice this form of contraception for 30 years without some danger? The answers are clearly not known. The indiscriminate prolonged use of these products should be discouraged.

Pregnancy Test

All of the products—progestational and combination progesterone-estrogen—will serve this purpose. Two products are approved by the Federal Drug Administration for this indication only, Gestest and Produosterone. For this purpose it might be better to use the higher dosages over a three day period in order to get a more rapid decidua-like reaction.

The advantage of this test over the biological tests is in its lower cost and the simplicity of the technique requiring no laboratory involvement.

Threatened Abortion—Habitual Abortion

Theoretically, the straight progesterones should be more efficient in these areas than the combination products. On the premise that abortion is often the result of inadequate corpus luteum action and decreased progestin production by that body, the supplying of progestational agents should act to prevent the inadvertent loss of a pregnancy.

In the patient threatening to abort, the use of the progesterones during this danger period is said to forestall the accident. There are, of course, certain concomitant precautions at this time (rest in bed, abstinence from coitus, sedation) and the question always arises as to which part of the treatment is the most efficacious. The etiology of abortion is varied and each patient must be individualized with an attempt to exclude anatomic causes (incompetent cervical os, uterine fibroids, uterine displacement, ovarian tumors). It must be remembered, also, that about one-third of all early abortions are ascribed to blighted ova. In this area, the use of the progesterones may prove to be very confusing. It is often most difficult to decide if an abortion is threatened, inevitable, incomplete or completed. Using the progesterones in such clinical situations may stop the bleeding but can result in a missed abortion with retention of a dead pregnancy within the uterus. The only way to determine whether this has or has not occurred is to wait for the growth of the uterus. Some manufacturers claim that their products will not support a missed abortion.

The use of the progesterone-estrogen products in the treatment of threatened abortion is recommended by many. The feeling is that the combination allows for maintenance of a more normal decidua. Recent reports tend to lean toward the straight progesterone treatment. In my experience, the use of the combined hormones has created greater problems in the area of missed abortion than have the progesterones alone.

In habitual abortion, after anatomic and genetic factors have been ruled out, the progesterone is used throughout the pregnancy in increasing dosages. At this point we must consider the androgenicity of the progesterones. Some of them are derived from and closely related to testosterone. A few reports refer to masculinization of a female infant as a result of the use of these products and some even report hirsutism in the mother. Although these side effects are reversible after the birth of the baby, their occurrence could be annoying.

Infertility

Again we must exclude as much as possible all factors which may be responsible for the difficulty in conception. Finding no obvious cause for the infertility and on the hope that it may be the result of a fertilized ovum not finding an adequately prepared endometrium, the progesterones will provide a better bed for implantation. Since the progesterones do not always cause suppression of ovulation their use in this situation is recommended by many.

The progesterone-estrogen combinations are used differently for this indication. There is no chance for pregnancy while these products are being used. They are taken cyclically for 3 months. According to some reports, the patients then will have what is called the "rebound phenomenum" which will bring back a better endometrium and make the environment more receptive to the implantation of a fertilized ovum.

Dysmenorrhea

Since progesterone is an agent supposed to decrease uterine contractility, it is recommended for use in the treatment of idiopathic dysmenorrhea. Again, we must exclude all anatomic and psychologic causes of this symptom before resorting to the use of these drugs. Progesterone may be used in the last half of the cycle for this purpose. Or, the progesterone-estrogen combinations can be used cyclically for three months to eliminate normal menstrual physiology hoping for an alteration in the pain producing mechanism when normal physiology is restored. Of course, if normal menstruation is prevented by drugs the dysmenorrhea will not occur.

Menstrual Irregularities

When anatomic abnormality has been ruled out one can regulate the menstrual cycle by the use of the progesterones cyclically. Either the straight progesterones or the combinations can be prescribed for this purpose. After three to four months of this therapy the normal physiological endocrinology is said to take over and operate more efficiently than it had before medication had been instituted. Although this empiric sort of treatment is not generally recognized as good medical practice it is, at times, necessary to take empiric or bold action in order to resolve a problem even temporarily.

Premenstrual Tension

We are all acquainted with this syndrome which becomes more aggravating as women approach the menopause. The complaints of bloating, excessive breast swelling, edema with gain in weight, backache and increased irritability occur in the second half of the cycle and are relieved when menstruation ensues. These symptoms are directly related to fluid retention which is a property of the steroids in general. The theory behind the use of these hormonal products in this area is that at this age there is a diminution of the natural production of the estrogenic and corpus luteum hormones. Thus, replacement should take care of this deficit.

In my experience, the use of steroids at this time generally tends to make the patient worse because of the further fluid retention engendered by these agents.

Endometriosis

This condition being that of ectopic endometrium, pain is produced when menstrual bleeding takes place within these areas. The use of these agents in preventing ovulation results in the lack

of formation of a secretory endometrium, and the production of a pseudo-pregnancy endometrium which does not bleed. Therefore the pain is reduced and the patient is more comfortable.

The use of either of the types of medication with which we are dealing will achieve this objective. This treatment is carried out continuously for a period of six to nine months. During this time there may be a regression in the endometriosis which may not become bothersome for some time after the cessation of therapy. I have found the use of these agents to be of value in the control of the pain and dysmenorrhea associated with endometriosis.

Adenocarcinoma of the Fundus Uteri

Palliation of fundal adenocarcinoma can be obtained by using massive doses of straight progesterone. The best results are obtained in patients with remote metastases, especially in the lung, which respond by shrinking and even disappearing in some instances. Local spread of the disease is apparently not affected. Patients with distant metastases have been maintained in relative comfort for from three to five years but eventually the disease proves fatal.

SIDE REACTIONS

Nausea and vomiting are a frequent result of the use of these drugs, especially the progesterone-estrogen combinations. With the reduced dosages now being used for contraception this annoyance is less common but occasionally patients must discontinue therapy because of this. These symptoms may become gradually less annoying as the use of the medication is continued. A change from one drug to another may accomplish a similar result.

Fluid retention and weight gain occurs almost invariably. Many patients who struggle to maintain a constant weight are disturbed by the five to ten pound weight gain during the time they use these drugs. When cyclic use for contraception produces this weight gain, it is generally not completely lost during the lay-off period. Oral diuretics may be of some value in helping control this problem.

Breast enlargement and engorgement is very common, particularly when the combination drugs are used. In addition there is tenderness or pain and nipple soreness. Since estrogen stimulates breast tissue, this action of the medications is to be expected. When the drugs are stopped the breasts do not return to their original state for a long time, if ever.

Break-through bleeding is described as bleeding from the uterus during the course of medication. This is of no significance, neither representing menstruation or lack of safety in contraception. It means only that dosage is insufficient to support the endometrium and increasing the dosage for several days will overcome this problem.

We have previously mentioned the masculinization of the female fetus and mother and feminization of a male infant ascribed to the use of the progesterones. These are so uncommon as to present no true contra-indication to the use of these agents.

CONTRA-INDICATIONS

Cancer of the breast and the genital tract, except for the corpus adenocarcinoma mentioned above are contra-indications to the use of these drugs. Although no cancer in humans has been proved to be produced by these agents, their use is felt to be a possible stimulus to the growth of some tumors.

Uterine fibroids are stimulated to growth by estrogens. So, in the presence of these tumors, the use of these drugs is contra-indicated.

These drugs have been accused as etiologic agents in the production of thrombophlebitis. Nothing has been proved in this respect but it may be wise, if in the presence of history of thromboembolic phenomena these drugs not be used.

REVIEW ARTICLE

LEAD POISONING:
Surveillance 1959-1964

Joseph R. Christian, M.D.[1]

During the past ten years the industrial consumption of lead in the United States averaged slightly over 1,000,000 tons per year. Approximately 40% was used in chemical compounds such as white lead, red lead, litharge, black oxides, lead silicates, lead chromates and tetraethyl-lead. The remaining 60% was consumed in metallic form as pure lead or as an alloy.

The industries consuming lead in large quantities are numerous. They include those involved in storage battery manufacturing, oil refining and gasoline, cable construction, paint and varnish production. The largest user is the storage battery industry, with over 350,000 tons of annual lead consumption.

There is a natural occurrence of lead in our soil, water, food and ambient air. Most humans eat, drink and inhale lead each day of their lives. This constant exposure results in a range of intake of 0.1 to 0.6 mgm. daily with a mean of 0.33 mgm. This precludes the presence of detectable quantities of lead in tissues, organs, feces and urine in persons without evidence of intoxication. Approximately 5% to 10% of ingested lead is excreted via the alimentary tract. The daily fecal output averages 0.3 mgm. and the urinary output 0.03 mgm.

Exposure to increased quantities of lead, alteration in the equilibrium of output and intake, or imbalance of homeostasis of the host with excessive tissue accumulation can result in the production of signs and/or symptoms of intoxication. The diagnosis of intoxication can be suspected when one or more of the following are present: 1. History of Pica 2. X-ray evidence of radio-opaque material in the GI tract 3. X-ray evidence of lead lines at the metaphyseal ends of the long bones 4. Elevated blood or urine lead level 5. Central nervous system signs or symptoms 6. Vomiting and/or other gastrointestinal disturbances 7. Positive test for coproporphyrin III in the urine 8. Reducing substance in the urine 9. Anemia 10. Basophilic stippling of red blood cells.

Items 1, 2, and 3 constitute suspicious evidence of lead poisoning; 4 (blood and urine levels) can be considered as equivocal, and 5 through 10 are signs, symptoms, or laboratory evidence strongly indicating lead intoxication.

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TABLE I—INCIDENCE OF LEAD POISONING

Year	Accidental Poisonings	Lead Poisonings	% of All Cases Accidental Poisoning Dying	Comparison % of Deaths Being From Lead Poisoning
1959	3,156 (22)	159 (21)	5%	(95%)
1960	3,254 (35)	153 (30)	4.7%	(86%)
1961	3,443 (28)	117 (16)	3.4%	(57%)
1962	3,828 (27)	154 (22)	4%	(81%)
1963	4,553 (30)	203 (19)	4%	(63%)
1964	4,664 (18)	140 (8)	3%	(44%)
TOTAL	22,898 (160)	926 (116)	4%	(71%)

( ) Number of Deaths.

During the six year period from January 1, 1959 through December 31, 1964 a total of 22,898 cases of accidental poisoning was reported to the Poison Control Center of the Chicago Board of Health. The total number of cases of lead intoxication during this same period was 926 or 4% of the total.

In July 1963 the City Council of the city of Chicago passed a resolution " . . . that it shall be the duty of every physician, dentist, other practitioner, hospital, attendant, nurse, laboratory, parent, householder, school authority, or any other person having knowledge of a known or suspected case of lead poisoning, in the city of Chicago, to report promptly such case, suspected case, or death in writing or by telephone to the Chicago Board of Health."

Total deaths due to accidental poisoning for the six year period were 160. The mortality from lead intoxication was 116 or 71% of the total deaths due to accidental poisoning. (Table 1)

Pica or the indiscriminate ingestion of non-edible substances was significantly related to lead poisoning. In the 926 reported cases 575 or 62% indicated the presence of pica with the ingestion of lead containing material. (Table 2)

The highest incidence and the highest mortality rate of reported cases was between the ages of one year and three years. Four cases were reported under one year of age; 375 (43 deaths) were one year of age; 367 (56 deaths) were two years of age; 119 (13 deaths) were three years of age; and 31 (3 deaths) were four years of age. Only one death (age 6 years) occurred over four years of age. (Table 3)

The peak periods of incidence occurred consistently during the months of June, July, August and September. The mortality rate paralleled the peak monthly incidence. (Table 4)

The sex distribution was not significant. However, the race distribution is delusive insofar as the areas involved in this survey were primarily non-white. (Table 5 and 6)

In 1962 a pilot survey of 1500 children was undertaken by the author in three

TABLE 2—RELATIONSHIP OF PICA TO LEAD POISONING

Year	Pica with Lead Ingestion	Pica without Lead Ingestion	Inhalation	Unknown	Denied	Total
1959	98	2	17	42		159
1960	94	—	—	59		153
1961	64	9	—	44		117
1962	92	4	—	58		154
1963	156	13	—	23	11	203
1964	71	3	—	55	11	140
TOTAL	575	31	17			926

TABLE 3—AGE DISTRIBUTION OF PATIENTS WITH LEAD POISONING

Age (Years)	1959	1960	1961	1962	1963	1964	Total
Under 1	1	—	1	—	1	1	4
1	62 (5)	70 (14)	48 (6)	63 (10)	82 (5)	50 (3)	375 (43)
2	55 (12)	59 (14)	50 (7)	64 (10)	91 (11)	57 (2)	376 (56)
3	17 (2)	19 (2)	11 (1)	23 (2)	25 (3)	24 (3)	119 (13)
4	11 (1)	5	6 (2)	2 (0)	2 (0)	5 (0)	31 (3)
5	7 (0)	—	1 (0)	2	—	1	11 (0)
6	1 (1)	—	—	—	1	1	3 (1)
7	2	—	—	—	1	1	4
8	1	—	—	—	—	—	1
9	2	—	—	—	—	—	2
Unknown	—	—	—	—	—	—	4
TOTAL	159 (21)	153 (30)	117 (16)	154 (22)	203 (19)	140 (8)	926 (116)

( ) Number of Deaths.

areas of the city of Chicago, using urinary coproporphyrin as a screening test for lead intoxication. The conclusions of this report were: 1. The clinician with a high index of suspicion can use the urinary coproporphyrin test as a presumptive test for lead intoxication. 2. Whenever this test is positive it is imperative that sufficient diagnostic studies be completed so that accurate categorization of the patient can be made. These are: a) No evidence of significant exposure b) Evidence of significant exposure without demonstrable tissue accumulation c) Evidence of significant exposure and early tissue accumulation without need for treatment d) Evidence of significant exposure and tissue accumulation requiring treatment.

In February 1963, the urinary coproporphyrin screening program was initiated in the city of Chicago. Six Chicago Board of Health Welfare Stations were selected from anticipated high incidence areas. Nurses were instructed to collect specimens and parents were prepared by letter and conferences to participate. A pick-up service was established so that there would be daily collection of specimens from the various Stations. The tests were completed in the laboratory located at Presbyterian-St. Luke's Hos-

TABLE 4—Seasonal OCCURRENCE OF LEAD POISONING

Month of Occurrence	1959	1960	1961	1962	1963	1964	Total
January	—	—	2	6	2	2	12
February	—	1 (1)	3	2	1	3	10 (1)
March	—	2 (1)	2	2	5	5	16 (1)
April	—	2	2 (1)	7	5 (1)	3	19 (2)
May	2 (1)	—	5 (1)	26 (3)	5 (1)	14	52 (6)
June	29 (6)	18 (4)	15 (1)	21 (5)	34 (3)	24 (2)	141 (21)
July	32 (6)	43 (10)	31 (4)	22 (4)	69 (8)	27 (2)	224 (34)
August	35 (4)	47 (7)	20 (4)	33 (5)	51 (4)	23 (3)	209 (27)
September	24	24 (7)	29 (4)	26 (4)	16 (2)	18	137 (17)
October	13	8	5 (1)	5	7	8 (1)	46 (2)
November	4 (2)	5	2	4 (1)	3	5	23 (3)
December	20 (2)	3	1	—	5	8	37 (2)
TOTAL	159 (21)	153 (30)	117 (16)	154 (22)	203 (19)	140 (8)	926 (116)

( ) Number of Deaths.

TABLE 5

Sex Distribution	1959	1960	1961	1962	1963	1964	Total
Males	75 (9)	82 (15)	56 (6)	86 (12)	102 (8)	68 (2)	469 (52)
Females	84 (12)	71 (15)	61 (10)	68 (10)	101 (11)	72 (6)	457 (64)
TOTAL	159 (21)	153 (30)	117 (16)	154 (22)	203 (19)	140 (8)	926 (116)

( ) Number of Deaths.

TABLE 6

Race Distribution	1959	1960	1961	1962	1963	1964	Total
Non-white	139 (19)	141 (24)	97 (12)	123 (16)	175 (15)	119 (6)	794 (92)
White	10 (2)	11 (6)	20 (4)	31 (6)	28 (4)	21 (2)	121 (24)
Unknown	10 (0)	1 (0)	—	—	—	—	11
TOTAL	159 (21)	153 (30)	117 (16)	154 (22)	203 (19)	140 (8)	926 (116)

( ) Number of Deaths.

pital under the direction of the author. The method used for the qualitative urinary coproporphyrin test is an adaptation of the procedure of Schwartz described in the Journal of Pediatrics, Vol. 56, No. 6, pp. 759-767, June 1960.

The specimens were collected in special one ounce containers which can be tightly capped for transportation.

In July 1963, the service was extended to include all of the Chicago Board of Health Infant Welfare Stations thereby allowing the screening service to be accessible to all residents of Chicago with children in the pre-school and school age groups.

A definite correlation has become evident: i.e., trace, one plus and two plus urinary coproporphyrin cannot be interpreted as indication of lead intoxication; nonetheless, the three plus and four plus cases have consistently proven to be correlated to lead intoxication.

The number of positive specimens collected during 1964 were as follows:

	1+	2+	3+	4+
January	—	—	—	—
February	—	—	—	—
March	—	—	—	—
April	—	—	—	—
May	4	6	2	2
June	2	—	2	—
July	29	23	18	6
August	25	13	7	1
September	21	5	2	2
October	10	8	5	3
November	7	6	7	2
December	5	4	2	—
TOTAL	103	65	45	16

All of the three plus and four plus patients were evaluated as follows:

1. A complete physical examination including a neurological examination was performed by a pediatrician.

2. X-rays of the abdomen and metaphyseal ends of long bones were taken.

3. A complete blood count including basophilic stippling was performed.

4. Urinalysis (complete) and repeat urinary coproporphyrin were done.

5. If physical examination, x-rays or laboratory studies confirmed the suspicion of lead intoxication the patient was referred to a hospital for treatment, whether or not signs and/or symptoms were present.

6. All children under 5 years of age, residing in the building in which an occupant was found to have a positive urinary coproporphyrin test, (trace, 1+ and 2+ included) were requested to also have a urinary screening test.

7. Each of these dwellings was inspected by a Chicago Board of Health Nurse.

8. If the nurse found any evidence of neglect of building maintenance she reported it to the Building Commission.

9. The Building Commission delegated an inspector to inspect the premises and any lack of compliance with building and maintenance codes which resulted in infringement on the health and welfare of an occupant was reported. Unless this deficiency was corrected within a reason-

able time the building was condemned for occupancy.

CONCLUSION

This report describes the multiphasic public health program of rigorous control of lead poisoning in the City of Chicago.

Accidental poisoning is the result of the inadequate use of available facilities, personnel, communication, education and even the law. Lead intoxication because of its high morbidity and mortality in the pediatric age group must be recognized prior to the time of production of signs and/or symptoms.

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ABSTRACTS AND REVIEWS

OF PUBLICATIONS BY THE STAFF

Dual-Rate Pacemaker. R. A. Carleton, W. Sessions and J. S. Graettinger: *The Journal of Thoracic and Cardiovascular Surgery, Vol. 48, No. 4, pp. 684–689, Oct., 1964*

Fixed rate implantable pacemakers of proved clinical effectiveness have recently been the mainstay of the long term treatment of symptoms due to complete A-V block. Physiologic advantage during stress is thought to accrue from paced rates 20 to 30 beats per minute above the usual fixed rate of approximately 70.

The present report describes a unit incorporating two pacemaker oscillator circuits which permit setting the pacemaker at either of two rates: e.g., 70 and 100. Switching from one rate to the other in the subcutaneously implanted unit is performed by throwing a switch with an externally applied magnet.

The effect of Neonatal Thymectomy in the Dog. N. L. Tilney, E. J. Beattie, Jr., and S. G. Economou: *Jour. of Surgical Research, Vol. 5, No. 1, pp. 23–30, Jan. 1965.*

The dog, unlike many species of laboratory animals, is thought to be immunologically mature at birth. Some investigators feel that the thymus gland has performed its major function in utero, and that neonatal extirpation of the gland fails to alter the immunobiology of the puppy. The results in the animals in this experiment parallel remarkably those recognized in the small laboratory rodents which themselves have undergone thymectomy. Several weeks after removal of the gland, the puppy becomes wasted, hunched and cachectic. The number of circulating peripheral lymphocytes and gamma globulins diminishes markedly within two weeks after operation when compared to similar animals with sham thymectomy. At postmorten examimation, the lymphoid tissue of the dogs with thymectomy showed decrease in numbers of lymphocytes and germinal centers. Because of the profound physical, hematologic and histologic alterations found in this study, we feel that the lymphoid system of the dog is less mature at birth than previously thought. These changes warrant further investigation in this species.

Anticoagulant Therapy. J. H. Olwin and J. L. Koppel, *Am. J. Nurs. 64: 107, 1964.*

Anticoagulant therapy in its present form has been used for approximately two decades. As the term implies, it is the cautious interference with the normal or perhaps abnormal clotting mechanism in an attempt to lower the clotting tendency of the patient's blood without contributing to unusual bleeding. Although the ideal method of anticoagulant therapy has not as yet been reached, there have developed during the last two decades routines which in the hands of experienced clinicians have given a certain amount of protection to individuals with various types of thromboembolic conditions.

This paper presents certain theoretical and practical aspects of anticoagulant therapy as they are understood at the present time. They are discussed under the following headings: Types and properties of anticoagulants, indications for anticoagulant therapy, the blood coagulation mechanism, methods of control, routine of administration, complications of anticoagulant therapy, long-term anticoagulant therapy, factors influencing uniformity of control, countermeasures, and decontrol.

Effects of Gastric Hyperthermia on Gastric Acid Secretion in the Dog. R. P. Rosswick, (London), S. Economou, and E. J. Beattie, Jr.: *Surgery, Vol. 55, No. 4, pp. 559–563, April, 1964.*

The recent work of Wangensteen and his group on the use of cold in the stomach reawakened interest in the effects of physical agents on the stomach. The effects of heating have been investigated only sporadically. This paper reviewed the past history of gastric hyperthermia and reported a series of experiments.

Gastrostomies were performed in dogs. Baseline acid studies before and after maximum histamine stimulation were obtained. The dogs were allocated to one of our four treatment groups consisting of 10 minutes or 20 minutes of 5°C or 10°C rise in gastric temperature. Following the hyperthermia gastric secretions were studied weekly for nine weeks. Heating at 5° above the normal gastric temperature produced a slight rise in total gastric acid secretion, with a tendency for the level of secretion to vary more than normal. There was no change in volume. Significant changes were found in dogs heated 10°C for 20 minutes. Both free and total acid were reduced to approximately 60 percent of the control level. There was also a significant decrease in the volume of secretion, but the volume returned to normal within six weeks.

Personality Traits in Caesarian-Normally Delivered Children. W. J. Pieper, E. E. Lessing, and H. A. Greenberg: *A.M.A. Archives of General Psychiatry, Vol. 11, p. 466, Nov. 1964.*

This study compared caesarian and normally delivered children in a large number of personality attributes falling under the general rubric of ego development.

The basic procedure was a retrospective analysis of case material collected over a ten year period at the Institute for Juvenile Research. Data on 300 variables were available on IBM punch cards for over 6,000 cases; 188 of these 6,000 cases were delivered by caesarian section. A matching case for each child in the group of 188 caesarians was selected from a pool of 3,000 cases which had been delivered vaginally without complications. Age, sex, race, ordinal position and father's occupation were used as matching variables. Comparisons were made in 76 variables including developmental data, psychological test findings, psychiatric symptomology and nature of the EEG pattern. The X^2 was utilized to test the significance of the differences between the two total samples and between subgroups based on age and sex. The null hypothesis of no difference between the normally and caesarian delivered groups was accepted.

Carcinoma of the Gallbladder. E. L. Strohl, W. G. Diffenbaugh, and R. W. Alexander: *Medical Times, Vol. 92, No. 11, pp. 1189–1194, Nov. 1964.*

The bizarre symptoms of carcinoma of the gallbladder preclude early diagnosis, but it is almost always associated with stones in the gallbladder.

It should be considered a preventable disease, since it occurs, almost invariably, in the patient having long-standing calculus cholecystitis.

Many theories have been presented as to the cause of the disease, which include irritations from gallstones, the carcinogenic action of bile salts and acids, and the malignant degeneration of papilloma of the gallbladder wall.

Carcinoma of the gallbladder originates, most commonly, in fundus or neck of the viscus, and rarely in the cystic duct; is spreads diffusely throughout the upper abdomen.

A consistent pattern of symptoms does not exist. Change in the character of the patient's symptoms was frequently the first manifestation of the disease. The pain was described as a constant, penetrating distress, in contrast to the usual intermittent colic of gallbladder disease.

More than sixty-five hundred deaths, due to carcinoma of the gallbladder, occur annually in the United States. This is an incidence of 4.5 per cent of all deaths due to carcinoma. More will develop as the life span of man continues to increase.

The results of surgery are poor, except in the low grade tumors limited to the mucosa.

The incidence of carcinoma of the gallbladder may not in itself justify cholecystectomy in patients having stones; however, the combined incidence of complications of calculus cholecystitis is justification for cholecystectomy, once calculus cholecystitis is diagnosed.

Mithramycin in the Treatment of Embryonal Cancer. S. KOFMAN, T. J. MEDREK and R. W. ALEXANDER: *Cancer, Vol. 17, No. 7, pp. 938–948, July 1964.*

Mithramycin is an effective chemotherapeutic agent against a variety of embryonal cancers. In a number of cases, it has been characterized by a low chemotherapeutic index in that there has been a narrow margin between the dose causing regression and the dose level associated with toxicity. Despite this, complete and long-term regression has occurred in patients with embryonal cancers. A regimen of therapy outlined in "Mitramycin in Treatment of Disseminated Cancer" allows for the prediction of the onset of serious toxicity. Some of the best therapeutic results have occurred with smaller doses. Further progress may be made by studying the mechanisms of toxicity, treating patients earlier, and perhaps developing analogues that have a higher chemotherapeutic index.

Pemphigus of the Larynx. L. J. WALLNER and R. W. ALEXANDER: *The Laryngoscope, LXXIV, No. 4, pp. 575–586, April 1964.*

In these five patients with prolonged superficial ulceration of laryngeal and oropharyngeal mucosa, the histologic diagnosis was confirmed in only three. Pemphigus was considered the most likely in all five.

The definitive histopathologic finding of acantholysis may be most difficult to obtain. Repeated biopsies may be necessary, and this may not be feasible in the larynx.

Where the history and gross findings are characteristic, and the histopathology consistent with pemphigus, even though acantholysis is not found, steroid therapy should be started. This is true, because the earlier in the disease the drug is started, the more readily pemphigus is controlled, and the longer the period of remission.

The Role of Paratenon in Healing of Experimental Tendon Transplants. J. H. SCHNEEWIND, I. K. KLINE, and C. W. MONSOUR: *Journal of Occupational Medicine, Dec. 1964.*

Paratenon is a specialized areolar connective tissue surrounding tendons which pull in a straight line. Its function is to provide blood supply and enhance the tendon gliding mechanism. This experiment was designed to examine the role of the paratenon in healing of tendon transplants.

It was found that the rate of healing in tendon grafts without paratenon was chronologically delayed as compared to the controls with paratenon present. The tendons in which paratenon was removed showed marked ischemic necrosis of the entire transplant as well as the ends of the tendon stumps. There was a delay in the appearance of tenoblastic activity and in orientation of the fibroblastic tissue. A firm fibrous union appeared at seven weeks following operation. However, in animals sacrificed 15 to 30 weeks after operation there was still considerable fibrous scar tissue replacing large areas of the tendon graft. There were also numerous adhesions of the paratenon, most marked in the junctional areas.

The Psychologic Challenge in Automation. A. P. SOLOMON: *Archives of Environmental Health, July 1964, Vol. 9, pp. 72–81.*

Since automation is creating an ever increasing problem of nonwork in this country, the author offers as a solution the interweaving of the work day or week with what is ordinarily considered as nonwork activities, such as cultural and physical activities, and job training and retraining activities. An on-the-job program of education for the coming increased leisure will bring back to work its essential psychologic potential for self-fulfillment. Historic concepts of leisure are reviewed, as are psychologic factors involved in work, and their relatedness to the psychology of play. It is pointed out that some large industrial organizations are already concerning themselves with this by-product of automation, increased leisure. Work in its best sense is not just part of life; it is literally life itself. The plan submitted will give to work the potential to increase man's hope and desire for self-fulfillment.

THE EDITOR'S PAGE

If, "A picture speaks a thousand words," then surely, one in color must bring out every nuance in each word. For this reason we are pleased to be able to inaugurate the practice of using color at such times when it is essential to the optimum presentation of the subject.

The article in this issue titled "Fluorescence Microscopy: Some Clinical and Research Applications" by Dr. A. W. Holmes and Dr. Fredrich Deinhardt is an excellent beginning. It obviates the need for the authors to attempt to describe the colors of the rainbow or for the reader to attempt to visualize them from pictures in black and white. In the following issue devoted to a symposium on "The Eye," of which Dr. William Hughes will be the Special Editor, we expect to use color to similar advantage.

We wish to acknowledge at this time our appreciation to those who made this move toward excellence possible.

Another and even more pleasant announcement is the acquisition of Dr. Evan M. Barton of the Department of Medicine as Associate Editor. The Bulletin recognizes its good fortune in obtaining the services of this stimulating scholar and scientist and intends to put them to good use to the advantage of our readers.

Steven G. Economou, M.D.
Editor

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ELECTRON PROBE MICROANALYSIS OF HISTOLOGICAL SECTIONS

Arthur J. Hale, M.B., Ch.B., Ph.D., D.Sc., F.R.S. (E)[1]

INTRODUCTION

Quantitative cytochemical methods have an advantage over biochemical analysis in that they allow one to correlate the measurement of a particular cellular component with its microscopic localisation. The majority of such methods depend upon measurement of light absorption produced by strains specifically and stoichiometrically bound to components of high molecular weight within the cell or to the natural light absorbing or retarding characteristics of cell components. Little use has been made of spectra other than those of ultra-violet and visible light in cytochemical analysis. With the introduction of electron probe microanalysis in the fields of metallurgy and mineralogy it has been proved possible to identify and measure the elements within microscopic specimens from analysis of X-ray spectra emitted by the specimen. This method has been applied to biological material by a few investigators[1,4–9] but its full potential is yet to be realized.

With it one can detect any element in the periodic table down to the level of magnesium with a spatial resolution of 1μ and a sensitivity of 0.01%. At first sight this might not appear to be either a useful microscopic resolution or a good sensitivity. Consideration reveals, however, that an elementary concentration which might of the order of 0.0001%, or trace level, in a bulk biochemical sample might be as high as 0.1-1.0% in a few cells within the sample. A microscopic resolution of 1μ is still useful when investigating cells which commonly have a diameter of 8-20μ. The detection of an element by this method is, however, independent of the way in which the element is combined in a molecule. Thus detection of iron will not tell you whether it is present in haemoglobin, haemosiderin, or the ferrous or ferric form. This may or may not be a limitation. To illustrate how this technique can be used to gain useful information I wish to describe some of our experimental work.

The basis of the method is that a histological section of either fresh frozen or fixed material, or a smear, is placed on a thin film of supporting material stretched across a supporting ring. The preparation is then coated with a conducting layer to reduce its resistance. The coated preparation is then placed in what is basically an electron microscope column in which a fine beam or probe of electrons can be scanned across the specimen. The electrons scattered backwards from the specimen and the X-rays generated within it can then be collected by means of suitable detectors and the localization of the electron scattering and X-ray emission displayed on an oscilloscope. The scan lines of the oscilloscope are synchronised with the scan lines of the plates producing the scanning of the electron probe; thus the image of the scattered electrons, which reveals the surface topography of

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Presented as a special lecture to the Division of Surgery, Edward J. Beattie, Jr., Chairman

the tissue, and the image of the X-rays which gives the localisation of the elements, can be displayed. Full details of the method have been published.[5]

The electron scatter and X-ray emission pictures of iron in several inclusions of human spleen are shown in Fig. 1. The electron scatter shows the presence of several scattering bodies which may have a high density or a high surface profile, but the X-ray picture shows that only some of these contain iron. Fig. 2 shows the

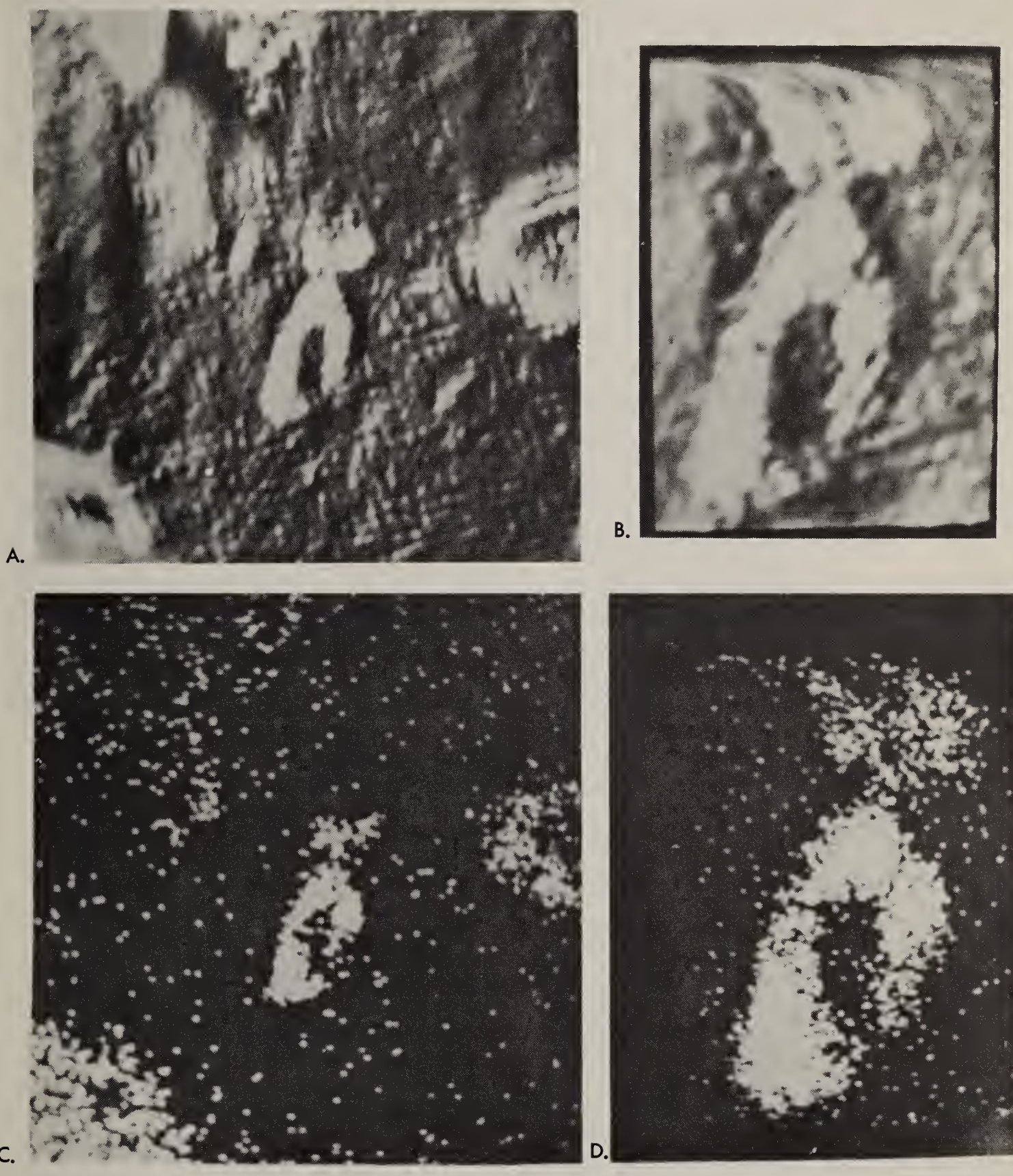
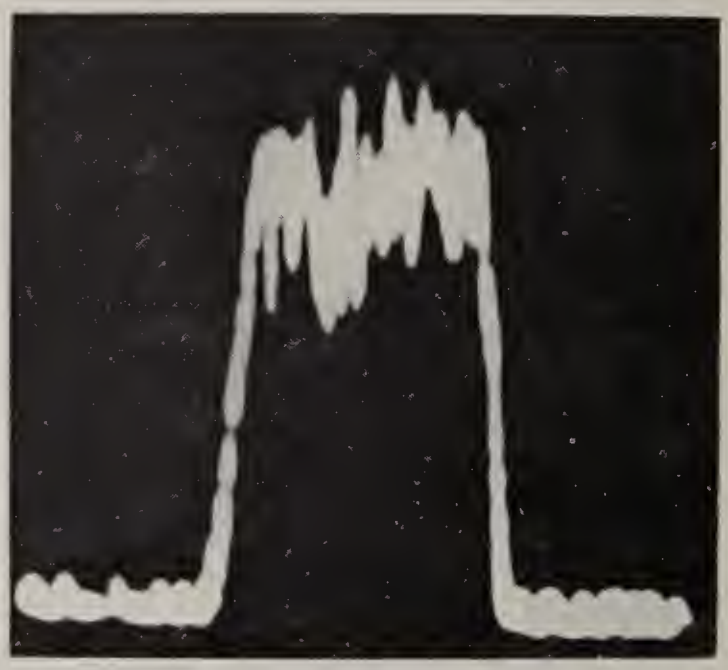


Fig. 1—Pictures (a) and (b) show the low and high-power electron back-scatter images of a 5μ thick section of human spleen which contained several inclusions of high density. Pictures (c) and (d) show the low and high-power photographic exposure caused by Ka emission for iron from these same areas. It can be seen that some of the electron scattering inclusions contain iron.

B.



D.

Fig. 2—(a) Reflected light picture of 5μ section of skin showing some sweat glands which were thought to be calcified. (b) Is the photographic exposure caused by Ka emission for calcium from the part of one of these structures shown in electron scatter picture (c). (d) Is the relative concentration of calcium along the line scan shown in (c).

reflected light, electron scatter, and X-ray emission pictures of a sweat gland which was thought to be calcified. The X-ray image and line trace across part of the specimen show that it is calcified. The advantages of such an analysis are:

(1) It is specific for each element.
(2) It is independent of molecular form and thus of the possibility of its detection being masked by atomic linkages.
(3) Detection is not hazarded by extraction during staining.
(4) Several elements can be examined in the same specimen.
(5) It permits measurement of the relative concentration of elements at different sites in the specimen.

The independence of detectability from the molecular combination of the element places some limitation on the method. Thus, for example, in the arterial wall the detection of sulphur does not permit one to say if it is sulphur in the amino acids of the collagen or elastic fibres or sulphur in the sulphated acid mucopolysaccharides of the ground substance. The microscope image does not resolve the anomaly as the sulphated acid mucopolysaccharides may be spread thinly over the surface of the fibrous component. It may, however, be possible to resolve this difficulty by staining the specimen with a method which is specific for acid mucopolysaccharides and gives a colour in the light microscope and which contains in the stain an element which can be detected by its X-ray emission. Such stains are alcian blue which contains copper and the dialysed iron method. Fig. 3 shows a section of arterial wall stained by the alcian blue method.

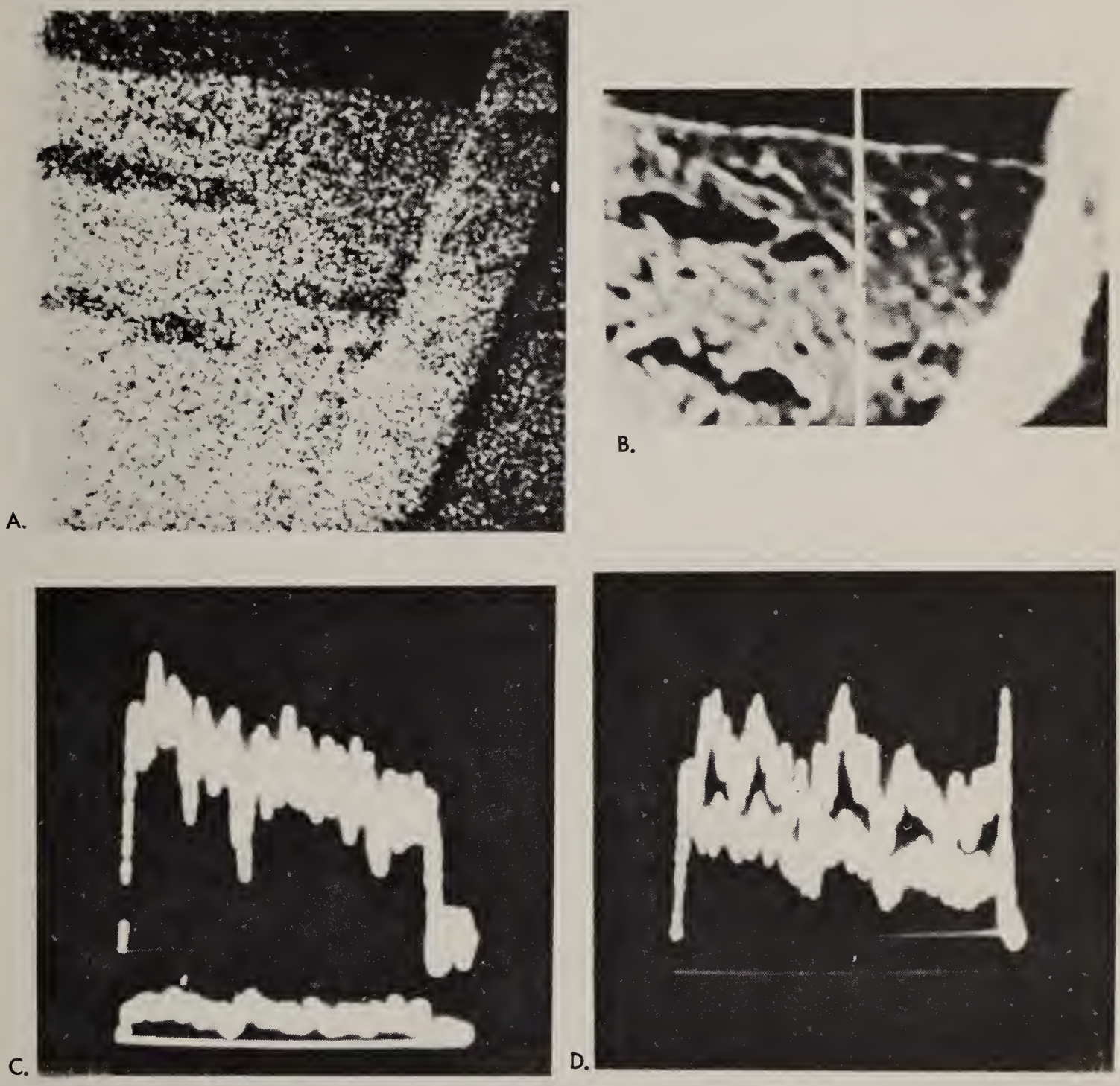


Fig. 3—A 5μ section of human aorta stained with Alcian blue and then examined using (a) the Ka emission for copper and (b) the electron back-scatter image. Picture (c) is the relative copper concentration and (d) the relative S concentration along the line indicated in (b). It can be seen that the signal/background ratio is inadequate in the S picture. The right hand end of each trace represents the upper intimal edge of the artery.

The copper emission picture suggests that the distribution of copper is relatively uniform throughout the specimen. The X-ray emission trace along the line shown in the electron scatter picture shows that the copper distribution is far from uniform. The sulphur emission trace along the same line shows that there is no obvious correlation between the sulphur and the copper distribution. Unfortunately detailed interpretation of such correlations with this stain proved impossible when it was realised that alcian blue contains sulphur as well as copper. Such correlations are, however, being continued with other stains. The advantages of using X-ray emission analysis instead of cytophotometry for measurement of the amount of "stain" bound to cellular components are:

(1) Small molecular sizes of "stain" can be used to extend the scope of designing cytochemical reagents.
(2) Correlations of "stain" and reacting component can be obtained in situ in some cases.
(3) There is a simple relation between amount measured and amount present in measuring the stain.
(4) The distribution of heavy metal "stains" detected by electron probe microanalysis can be correlated with the distribution of these metals at the electron microscope level.

A large number of cytochemical methods could be utilised in this way. Used by itself this approach is limited, but when the same specimen or a closely adjacent one is investigated by light microscopy after staining or by some other analytical method, then the scope is considerably extended.

The future of the method lies in using it for the identification and characterisation of particulate inclusions in microscopic samples of tissue where insufficient material is present for more conventional analysis, e.g. in the identification of the causative particles in pneumoconiosis. As a research method it should provide information on the distribution of iron, copper, potassium, calcium etc., in tissue and when used in conjunction with suitable staining methods may permit quantitation of the cellular components to which the stains are bound.

ACKNOWLEDGMENT

This work was carried out in conjunction with Drs. T. Hall, V. E. Switsur, and R. C. Curran of the Department of Pathology, St. Thomas's Hospital Medical School, London, and the Cavendish Laboratory, Free School Lane, Cambridge, under the auspices of the Medical Research Council.

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EFFECTS OF ANESTHESIA AND SURGERY ON LIVER IN MAN:
Preliminary Report

John R. Torgerson, M.D.[1], A. W. Holmes, M.D.[2], P. W. Searles, M.D.[3], and T. L. Ashcraft, M.D.[4]

INTRODUCTION

A variety of reports has been presented in the recent medical literature about the hepatotoxicity of various pharmaceutical agents. Among such reports a number can be found dealing primarily with a halogenated anesthetic agent, halothane. The stimulus for all these reports, about halothane as well as other anesthetic agents, has most frequently been severe liver derangement following surgical-anesthetic experiences. Most studies, both antagonistic and protagonistic to halothane, have been chiefly retrospective. Some say, in essence, that the severe liver disorder was due to this agent, because, by the process of elimination, none of the other well recognized causes could be well established[1,2]. Other studies review large series of surgical-anesthetic experiences and state that there was little, if any, difference in the incidence of liver dysfunction following use of various types of anesthesia[3,4]. The reports cite, as end points, almost exclusively extensive and severe liver disease.

Unfortunately, liver disorders can develop slowly from a variety of causes and lead to a cumulative deleterious effect. Such development is often insidious and difficult to recognize. The patient, without thorough preoperative evaluation, is a poorly determined variable.

The effects upon the liver of a presenting disease, which leads to surgical intervention, are accessible to evaluation, which should be the result of evidence not simply of surmise. This is essential if later conclusions about liver disorders are to be meaningful.

Often we are given a patient who is an imperfect point of reference for a beginning. We then administer to this patient a variety of drugs preoperatively, at surgery, and postoperatively. Tissues are manipulated and traumatized. Abdominal surgery[5] is frequently associated with laboratory test findings which might be construed as a deleterious effect upon the liver. The stresses of hypoxia, (during

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surgery and/or postoperatively) the responses associated with healing and homeostasis, the stresses of postoperative complications such as infection, cardiovascular depression and pulmonary disorders, all are difficult or impossible to measure accurately.

PURPOSE

It is our purpose to delineate the ranges of pre- to postoperative changes in liver function in patients undergoing surgical-anesthetic experiences. It is felt that if anesthesia or surgery can be responsible for initiating or activating massive and severe liver disorders, then lesser disorders of liver function, perhaps more frequent, might escape notice unless specifically searched for. Consequently, we have attempted to observe the presence or absence of changes in liver function as revealed by certain standard enzymatic and biochemical measurements.

METHODS AND MATERIALS

This study analyses and evaluates postoperative changes of liver function tests in randomly selected patients. The tests reported herein are the determination in serum of isocitric dehydrogenase (ICD), glutamic-oxaloacetic transaminase (SGOT) and total bilirubin. These tests were made preoperatively and on the first, second, and third days postoperatively. The anesthesiologists did not know which of their patients were in this study program; in this way, their choice of anesthesia and type or manner of administration was not biased. Blood samples were coded so that laboratory technicians did not know from whom a specific sample was obtained.

RESULTS

Categories of surgery are presented in Table 1. Note that a minimal amount of tissue manipulation can be expected in the operations done with local anesthesia. The halothane and cyclopropane anesthesias were supplemented with nitrous oxide and oxygen.

The SGOT determinations are summarized in Tables 2 and 3. In Table 2 it can be seen that the absolute findings postoperatively generally are higher than the preoperative levels. The incidence of abnormal postoperative determinations is similar among the various categories of surgery. The group using local anesthesia has the lowest incidence of abnormal findings and the narcotic-nitrous oxide group has the greatest. Note the great incidence of abnormal and high normal levels in the narcotic-nitrous groups in the preoperative as well as postoperative periods.

TABLE 1

Distribution of Types of Surgery
Associated with Various Anesthesias

Anesthesia type	No. of cases	Thoracic			Abdominal			Plastic	Eye	Extremities	Obst. Gyn.	GU	Neck
		Lung	Heart	Superficial	Upper	Lower	Superficial						
Halothane	86	6	4	4	11	7	4	2	2	8	10	19	10
Cyclopropane	60	1	0	5	16	12	6	0	0	3	14	1	2
Nitrous-narcotic	36	4	0	6	9	7	0	0	0	5	1	1	3
Regional	18	0	0	0	0	2	4	0	0	2	2	8	0
Local	34	0	0	0	2	3	2	3	17	1	2	2	2

TABLE 2

Glutamic-oxaloacetic Transaminase (SGOT)
(Normal levels to 45 units)

Anesthetic	No. of Cases	The distribution within each anesthetic group of absolute SGOT levels, both pre- and postoperatively; expressed as percentage of total number of cases per group.					
		Low Normal		High Normal		Abnormal	
		Pre-	Post-	Pre-	Post-	Pre-	Post-
Halothane	86	73%	51%	22%	35%	5%	14%
Cyclo-propane	60	85	50	8	34	7	15
Narcotic-nitrous	36	42	14	39	39	19	47
Regional	18	83	40	12	40	5	20
Local	34	78	60	19	28	3	12

TABLE 3

Glutamic-oxaloacetic Transaminase (SGOT)
(Normal levels to 45 units)

Anesthetic	Mean Postoperative Changes in SGOT Level expressed as percentage of total number of cases per group		
	Down	Up Less than 6 units	Up More than 6 units
Halothane	37	26	47
Cyclopropane	24	35	40
Narcotic-Nitrous	22	39	39
Regional	20	20	60
Local	44	25	31

Without regard for absolute abnormal levels, we record the direction and extent of changes between preoperative and postoperative values in Table 3. These figures compare the mean postoperative SGOT value from a single patient with his or her preoperative determination. A similar range of findings is seen for this enzyme in all five categories of anesthesia. This indicates a similar degree of change as opposed to comparisons based upon absolute levels.

In Table 4 and 5 the effects of surgery and anesthesia upon the ICD levels are illustrated. The incidence of abnormal findings postoperatively are illustrated. The incidence of abnormal findings postoperatively is not significantly different when the general and regional anesthetic groups are compared. Although the narcotic-nitrous-oxide group has a thirty-six percent incidence of abnormal findings postoperatively, the percentage of high preoperative levels was greater than in other groups. Note in Table 5 that the local anesthesia group, when compared to the other groups, has a significantly lower tendency for increasing levels of ICD after surgery. Even though the narcotic-nitrous group's incidence of abnormal findings is much higher than the other groups, its tendency to increase is similar to that observed in the other groups.

TABLE 4

Isocitric Dehydrogenase (ICD)
(Normal level to 250 units)

Anesthetic	No. of Cases	Pre- & Postoperative Enzyme Levels expressed as percentage of total number of cases per group					
		Low Normal		High Normal		Abnormal	
		Pre-	Post-	Pre-	Post-	Pre-	Post-
Halothane	86	40%	20%	50%	65%	10%	15%
Cyclopropane	60	49	24	45	56	6	20
Narcotic-nitrous	36	17	8	70	56	14	36
Regional	18	45	11	55	62	0	20
Local	34	34	28	60	63	6	9

TABLE 5

Isocitric Dehydrogenase (ICD)
(Normal level to 250 units)

Anesthetic	Mean Postoperative Changes of Enzyme levels expressed as total number of cases per group		
	Down	Up less than 13 units	Up more than 13 units
Halothane	40%	20%	40%
Cyclopropane	30	28	41
Narcotic-nitrous	39	8	53
Regional	18	27	55
Local	63	18	18

In Tables 6 and 7, the total bilirubin determinations are presented. The differences between the local group and the other groups is very distinct here. The local group has an incidence of preoperative abnormal levels similar to that of the other groups. After operation, the local group demonstrates no increase in the percentage of cases with elevated serum bilirubin determinations, whereas all other groups increased in percent of cases with abnormal value. In Table 7, no differences can be seen when the other groups are compared among themselves except within the narcotic-nitrous group. In this group, instances with a greater than average increase from the preoperative levels are very few. Interestingly, blood replacement in the narcotic-nitrous cases was often with plasma and infrequently with whole blood.

Table 8 deals with the ranges and the means of pre- to postoperative changes. Note the relatively small magnitude of the means of the changes. When abnormalities do occur, these can most frequently be explained on the basis of present disease or associated procedures. Frequently metastatic neoplastic disease, pre-existing liver pathology, severe cardiovascular disease, regional enteritis, and abdominal operations (chiefly upper abdominal) are associated with the greater increases of levels of these determinations in a given patient.

TABLE 6

Total Serum Bilirubin
(Normal levels of 0.3 to 1.0 mgm./100 ml)

Anesthetic	No. of Cases	Pre- & Postoperative Levels of Total Serum Bilirubin expressed as percentage of total number of cases per group					
		Low Normal		High Normal		Abnormal	
		Pre-	Post-	Pre-	Post-	Pre-	Post-
Halothane	86	67%	39%	27%	42%	6%	19%
Cyclopropane	60	68	47	25	42	7	11
Narcotic-nitrous	36	14	32	83	54	3	14
Regional	18	87	55	12	34	0	10
Local	34	63	53	34	44	3	3

TABLE 7

Total Serum Bilirubin
(Normal levels of 0.3 to 1.0 mgm./100 ml)

Anesthetic	Mean Postoperative Changes in Total Serum Bilirubin expressed as percentage of total number of cases per group		
	Down	Up less than 0.1 units	Up more than 0.1 units
Halothane	23%	30%	47%
Cyclopropane	18	34	48
Narcotic-Nitrous	18	76	6
Regional	29	29	41
Local	53	25	22

TABLE 8

Qualitative and Quantitative Changes Between Pre- and Postoperative
Total Bilirubins, SGOT and ICD Determinations in Patients Undergoing Surgery

ENZYME	Anesthetic				
	Halothane (86 cases)	Cyclopropane (60 cases)	N_2O-Narcotic (36 cases)	Regional (18 cases)	Local (34 cases)
SGOT (0 — 45 units = normal)					
Range of change (units)	−7 to+31	−2 to +34	−41 to +106	−16 to +30	−26 to +72
Average change (units)	+7.7	+7	+22.8	+6.7	+1.5
ICD (0 — 250 units = normal)					
Range of change (units)	−166 to +312	−4 to +155	−440 to −445	−57 to +208	−104 to +92
Average change (units)	+16	+15	+9	+26	−12
Total Bilirubin (0.3 to 1.0 mgm/100 ml. of whole blood)					
Range of change (mg %)	−0.28 to +0.90	−0.01 to .73	−0.30 to 0.80	−0.39 to 0.40	−0.31 to 0.27
Average change (mg %)	+0.15	+0.09	+0.19	+0.03	+0.06

DISCUSSION

Following major surgery, there is a general tendency toward increased levels of GOT, ICD and total bilirubin. This was not as apparent in the group receiving local anesthesia as it was in the other groups. This group experienced less surgical manipulation than the other groups. Anesthesia and its effects without any surgical trauma are being tested.

Among the three groups receiving a general anesthesia, very little difference between pre- and postoperative values is noted. The noteworthy exceptions to this were most often associated with remarkably high preoperative levels not described individually and in detail in this paper.

The narcotic-nitrous anesthesia group demonstrated minimal postoperative rises in total bilirubin values. Since, in this group, plasma instead of whole blood was frequently used, we suggest that this may explain the favorable findings. In contradistinction, this group had the greatest incidence of postoperative abnormal findings of ICD and GOT determinations. Proportionately it had a high incidence of abnormal and exceptionally high normal determinations preoperatively. We suggest that these findings are significantly related, viz. abnormal and very high normal preoperative determinations are likely to be abnormal postoperatively.

SUMMARY

Ranges of pre- to postoperative changes for GOT, ICD and total bilirubin have been presented. A general tendency for these ranges to shift to higher levels has been noted for the postoperative period following major surgery. No distinctive differences in alterations of liver function were noted among the anesthetic agents when they were used for major surgery and when no other apparent cause for alteration was present. These findings are in accord with those of others[6,7] and indicate that factors other than the use of the anesthetic agents studied are of major importance in postoperative liver damage. This does not eliminate the anesthetic agent as a contributive factor to abnormal liver function postoperatively.

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EXCITATION OF HOMOLOGOUS TISSUE IMMUNE MECHANISMS BY PRETREATMENT OF MATERNAL HOST WITH TISSUES OF ITS OWN EMBRYOS PRIOR TO GRAFTING

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INTRODUCTION

Previous experiments have domonstrated that it was possible to alert mechanisms injurious to homografts of adult musculofascial tissues in pregnant and non-pregnant rabbits by pretreatment of the recipients with leukocytes or whole blood from multiple donors other than donors of the grafts[1,2]. The homologous tissue reaction consisted of a fibro-collagenous encapsulation of the transplant with varying degrees of vascular penetration by the host in the curious absence of inflammation.

Other experiments have indicated that it was also possible to accelerate injury to homologous musculofascial grafts in non-pregnant rabbits by pretreatment of the recipient with pooled, crushed embryonic tissues (14-16 days of gestation) prior to grafting with adult musculofascial grafts from random donors (4). The modified homologous tissue reaction was identical to that observed in hosts receiving whole blood or leukocytes prior to grafting.

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The present experiments were designed to determine whether it was possible to stimulate mechanisms of homologous tissue immunity in the maternal host by injection of tissues from its own embryos before grafting with musculofascial transplants from random donors.

METHODS

Eighteen New Zealand white rabbits (weighing about 2.5 kilograms) were operated upon under Nembutal anaesthesia and with sterile precautions. In each experiment the embryos of a litter were recovered through small incisions in the antimesenteric border of the uterus. The uterine incisions were closed. A group of about eight embryos was pooled, crushed in a minimal volume of normal saline and injected directly into the erector spinae muscle through a small lumbar skin incision in the left side of the back of the maternal host. The right side of the lumbar region was prepared so as to expose the erector spinae. A cuboid mass of skeletal muscle measuring 15 mm. in length and breadth and 5 mm. in

thickness with attached fascia was resected and discarded. A musculofascial graft of comparable size was resected from a random adult donor and implanted in the previously prepared graft site in the maternal host. The graft was sutured in place with four monofilament nylon sutures. The panniculus carnosus and skin were closed, respectively, with plain catgut and nylon. Collodion was sprayed over the wound.

Two weeks later, the maternal host was killed by injection of procaine solution into the cisterna magna. The skin was removed from the back and a ventral incision was made in the abdomen. The carcass was then immersed in 10 per cent formalin. Following four days of fixation the embryonic and musculofascial transplantation sites were cut in serial thin blocks in a direction perpendicular to the muscle fascia. The consecutive blocks of tissue, including the residual transplant and all tissues adjacent to it, were prepared for microscopic study in sections stained with hematoxylin and eosin.

RESULTS

Gross examination of the homologous musculofascial transplants after fixation, showed that they were well-healed in place. A bursal sac had formed, as customary, over the fascia of the transplant. The floor of the bursal space consisted of a translucent pannus of granulation tissue arising from the host.

Gross examination of the embryonic tissue injection sites showed irregular, soft, dark areas within the skeletal muscle of the maternal host's erector spinae. In five instances the embryonic tissue injection sites were large and resembled tumor masses.

Microscopic examination of 15 of the homologous musculofascial transplants showed them to be well-healed in place. A pannus of well-vasculatized connective tissue had grown over the fascia of the transplant. Vessels had grown from the pannus down through the fascia to terminate in an angiomatous manner within the zone between the fascia and the skeletal muscle fibers of the transplant. Absorption of muscle fibers was curiously impaired in spite of the rich blood supply. Inflammation within the zone did not develop.

Microscopic examination of the remaining homologous musculofascial transplants showed a pattern of organization similar to the aforementioned with the exception of a mild lymphocytic infiltration within the narrow zone located beneath the fascia of the graft. This type of tissue reaction was considered to be a mild form noted in animals, which react feebly to pretreatment with homologous cells or in instances in which the amount of homologous cells has not been sufficient to immunize the animal.

Microscopic examination of the embryonic tissue sites showed fragments of cartilage, dermal and glandular elements embedded in a matrix of proliferating fetal skeletal muscle fibers. Occasional foci of lumphocytes were observed in and about the gradually resorbing embryonic tissues.

Embryonic tissue sites on microscopic examination showed evidence of organ structure in five instances of teratoma-like formation. Thymus tissue and renal tissue were observed.

COMMENT

The present experiments indicate that mechanisms of homologous tissue immunity can be alerted in the maternal host by injections of tissues from its own embryos prior to grafting with adult tissues. The accelerated destruction of the homograft in the maternal host was the same as that observed in maternal hosts pretreated with graft donor's blood (adult) prior to grafting.

Similar biological means designed to enhance deterioration of the concepti have not been successful. The experiments of Lanman et al. have shown that grafting of the female during pregnancy with parent male tissues does not adversely affect the concepti. Also, transfers of fertilized ova from a sensitized female

to a similarly sensitized female did not affect the survival rate within the litter[5]. In the same connection, our experiments involving the transfusion of the maternal host with blood from multiple adult donors did not promote premature placental aging[6]. The fact that homograft immunity can be transferred to the feti during pregnancy has been shown by Halasz et al.[7] In this instance the progeny showed the accelerated rejection phenomenon indicating the placental transmission of mechanisms of homologous tissue immunity.

More recently Osoba has shown that normal homologous tissue immune responsiveness can be restored in thymectomized female CBA mice by pregnancy.[8] These experiments point to the transplacental transmission of fetal thymic hormone which may be responsible for the conditioning of the maternal reticuloendothelial system.

While the present experiments add further credence to the reactivity of the extrauterine maternal tissue defense mechanisms to fetal tissue antigens, further studies are needed, not only to elucidate the underlying factors involved in the homologous tissue incompatibility system but also factors which contribute to the harmonious relationship between the opposed maternal and fetal tissues during normal pregnancy.

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ACUTE PYOGENIC ARTHRITIS:
A Review of 21 Cases

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INTRODUCTION

This comparative study of twenty-one cases of acute pyogenic arthritis was done in an attempt to determine an effective program of therapy. The study included cases of acute pyogenic arthritis of hematogenous origin, and those which had previous surgery or trauma and in which the wound was well healed prior to development of the infection. The study did not include cases of Neiserian or Tuberculous arthritis or cases in which joint involvement was not the predominant factor. It also did not include those cases in which the infecting organism was not known, unless there was gross purulence with negative cultures for fungi or there was an extremely rapid response to antibiotic therapy.

The mechanisms of implantation are listed below in Table 1.

It can be seen that the hematogenous mode was the most frequent. The micrococcus pyogenes variety aureus (coagulase positive) was the most frequent organism with one mixed infection of Staphylococcus aureus and β. hemolytic Streptococcus. (Table 2) Sensitivity studies were reported on all known organisms but four.

In Table 3, data was compiled regarding the site of infection, sex of the patient and age at onset. It can be seen that the knee is most frequently affected in this series, and that there was no significant predominence in either age or sex distribution.

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THERAPY

For purposes of comparison the cases were divided into four groups on the basis of fundamentally different methods of treatment. Exact grouping was impossible because of minor differences from case to case such as type of immobilization, dosage schedule, age, and organism sensitivity. In all cases but one the antibiotic used was the one to which the organism was most sensitive when this was known. Group IV includes one case in which the catheter was inserted through a #13 needle rather than by arthrotomy, and one case in which the patient received up to 10,000,000 units of penicillin intravenously for sixty days prior to arthrotomy.

Group I . . . . . 3 cases

These patients received systemic antibiotics plus immobilization of the limb involved.

Group II . . . . . **4 cases**

Systemic antibiotics were given. One to six aspirations of the joint were done on separate days with instillation of antibiotics in three of four cases. All were immobilized.

Group III . . . . . **4 cases**

Systemic antibiotics were given and drainage by arthrotomy was performed. Two had a primary closure and two were packed open with vaseline gauze. All were immobilized.

Group IV

These patients also received systemic antibiotics plus drainage by arthrotomy. In all cases, however, a polyethylene catheter was sutured in place, the wound closed primarily, and local antibiotics were instilled by catheter. All were immobilized. The usual dose of medication per catheter was two times the daily systemic dose in 250 cc of physiologic saline and divided into two hourly instillations.

TABLE 1

MODE OF INFECTION	NO. CASES
Hematogenous	14
Previous noninfected surgery	3
Puncture wound	3
Compound fracture ten years before	1

TABLE 2

ORGANISM	NO. CASES
Micrococcus pyogenes (var. aureus coag. pos.)	14
Micrococcus pyogenes (coag. neg.)	2
β. hemolytic Streptococcus	2
Pseudomonas aeruginosa	1
Unknown	3

TABLE 3

SITE	NO. CASES
knee	11
hip	6
elbow	2
wrist	1
hand	1
SEX	
Males	11
Females	10
AGE	
3 weeks	4
6 years	2
9-10	2
11-20	3
21-30	2
41-50	2
51-60	1
60 plus	3

RESULTS

The criteria used in the evaluation of joint infection were local signs, body temperature, white blood cell count with differential, sedimentation rate, culture of aspirate, and roentgenologic change. In this series the white blood cell count was usually 20,000 per mm^3 or less with a shift to the left, however, there was no rise in one infant and in one patient over sixty years of age. Similarly there was no fever in two infants. Local signs were frequently altered dramatically by surgery but also often the affected part was encased in a plaster cast making such evaluation difficult.

In Table 4 the range and average number of hospital days and the number of days of symptoms prior to treatment are tabulated for each group. Similarly, the number of days for temperature and white blood cell count to return to normal is listed.

TABLE 4

GROUPS		I	II	III	IV
Days to Normal	Temperature	7	6	10	9
	WBC.....	6	14	14	11
Hosp. Stay	(Average).....	22	38	88	49
	(Range).....	8-37	10-50	42-113	20-82
Symptoms Prior to Treatment	(Average).....	4	16	37	11
	(Range).....	1-10	4-42	14-90	3-36
Age	(Range).....	3 wks.-33 yrs.	3 wks.-22 yrs.	42-67 yrs.	3 wks.-64 yrs.
Responsible Organism	Staph. aureus (coag. +)	3	1	4	6
	Staph. aureus (coag. —).....	0	2	0	0
	β. hem. strep.....	1	0	0	0
	Pseudomonas....	0	1	0	0
	Unknown.....	2	0	0	1

CASE SUMMARIES

Group I

H.S. was a newborn with Staphylococcus aureus infection of the left hip. (Fig. 1a.) The patient had neonatal septicemia and was too ill to operate upon at an earlier date. One day after the onset of symtoms treatment was begun with penicillin, streptomycin, chloromycetin, and erythromycin. Two and one-half years later there was no evidence of active infection but she had 2 centimeters of limb shortening, an unstable hip, no formation of the femoral head on X-ray, and was being maintained in an abduction splint. (Fig. 1b.)

C. B. was a 46-year-old male with a Staphylococcus aureus infection of the left knee. The patient had psoriatic arthritis with effusion. Aspiration 3 months previously yielded clear liquid which was negative on culture. Penicillian and Erythromycin were begun five days after symptoms began. Three years later he was asymptomatic except for psoriasis and with no evidence of active infection.

B. F. was an 18-year-old female with staphylococcus aureus infection of the right hip. Treatment with penicillin and achromycin was begun two days after the onset of symptoms. Six months later she was asympotmatic as reported by telephone.

L. M. was a 33-year-old female with infection of the left wrist. The organism was not known. All other cultures, the latex fixation test and other studies were negative. She had an extremely rapid response to penicillin which was begun three days after the onset of symptoms. There is no long-term follow-up.

B. B. was a 16-year-old male with β. hemolytic Streptococcus infection of joints of the wrist. The patient also had lobar pneumonia. Intravenous penicillin was begun 10 days after the onset of symptoms and the infection was apparently controlled. There is no long-term follow-up.

F. V. was a 10-year-old female with an infection of the right knee, the organism not being known. All cultures including those for fungi were negative. One day following the onset of symptoms she was started on penicillin, streptomycin, and terramycin. Six months later she was readmitted for parasitic infestation at which time examination of the knee was negative. Two-and-one-half years later she had no orthopedic complaints and examination was again negative.

Fig. 1a—Antero-posterior roentgenogram of pelvis and both hips two weeks after the onset of symptoms.

Group II

K. D. was a six-year-old male with pseudomonas aeruginosa infection of the right hip. This patient also had leukemia. Systemic tetracycline and streptomycin were begun eight weeks after the onset of symptoms. The joint was aspirated four times and 1.5 gms. of streptomycin instilled each time. 4 months later the patient died of leukemia. At the time of death there was no active infection but the femoral head was absent radiologically.

G. C. was a 3-week-old infant with Staphylococcus aureus infection of the right knee. Systemic novobiocin and erythromycin were started 15 days after the onset of the symptoms and the joint was aspirated two times. No antibiotic was instilled. Ten months later there was no active infection, but there was 30 degrees of valgus at the knee and

radiographically malformation of the lateral aspect of the distal femoral epiphysis. Osteotomy was being considered.

D. B. was a 22-year-old female with Staphylococcal infection of the right elbow. Penicillin and tetracycline were started five days after onset of symptoms and the joint was aspirated four times. 250,000 units of penicillin were instilled each time. Sixteen months later there was a full range of motion and no positive local signs. The elbow was normal radiographically.

W. C. was a 9-year-old male with Staphylococcal infection of the right knee. Three weeks prior to treatment the patient suffered a puncture wound to the knee from a bed spring. Penicillin was started four days after onset of symptoms and the knee was aspirated six times with the instillation of 500,000 units of penicillin each time. Eighteen months later there was a full range of painless motion and the knee was considered clinically normal.

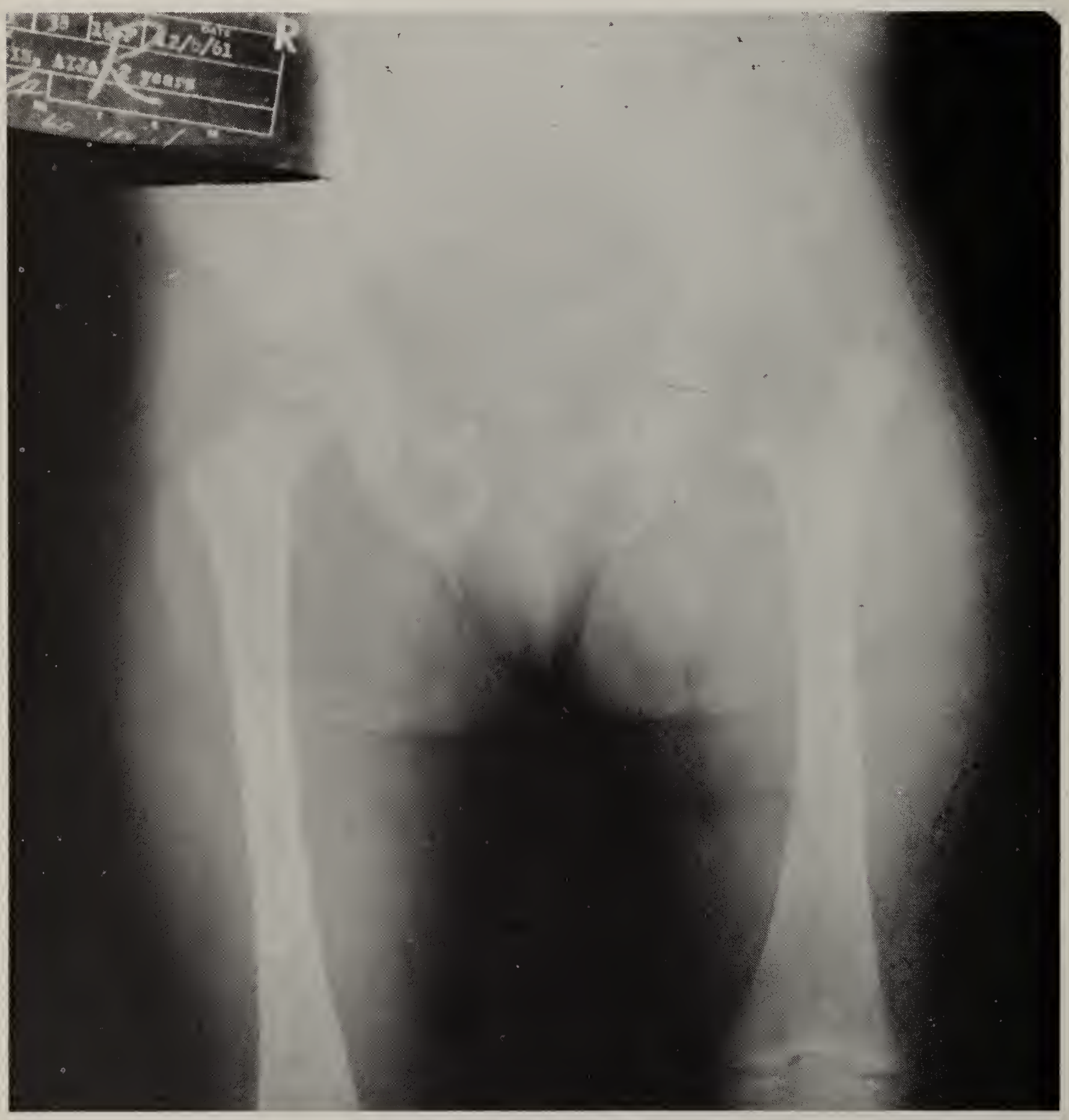

Fig. 1b—Similar view of pelvis of same patient at 2½ years of age.

Group III

O. C. was a 42-year-old male with Staphylococcus aureus infection of the right knee. Ten years previously the patient had a compound fracture of the knee which healed with no bony residual. Aureomycin and streptomycin were begun 28 days after the onset of symptoms and the patient had an arthrotomy for drainage with primary closure of the wound. Seven years later the patient had an occasional ache and slight decrease in the range of motion. There was radiological evidence of early degenerative arthritis but no active infection.

K. V. was a 63-year-old male with Staphylococcus aureus infection in the left knee. The patient had been treated for four months with Meticortin® elsewhere and systemic antibiotics were started 90 days after the onset of knee joint symptoms. He received penicillin, streptomycin, erythromycin, and tetracycline, and had an arthrotomy for drainage with a primary closure of the wound. Six months later he had a fusion for pain and cortical destruction. At this time there was no inflammatory process. Three years after his infection the fusion was solid and asymptomatic, however, he was having some pain in the ankle on that side.

E. M. was a 57-year-old female with a Staphylococcus aureus infection of the left hip. The patient previously had a fracture of the femoral neck with placement of an Eicher prosthesis on the infected side. She received erythromycin, chloromycetin, and novobiocin, and had an arthrotomy for drainage and removal of the prosthesis. This was packed open with vaseline gauze. Two days after discharge the patient suddenly expired. At post-mortem examination the cause of death was found to be a pulmonary embolism.

I. W. was a 67-year-old female with Staphylococcus aureus infection of the left hip. The patient previously had a fracture of the hip with closed reduction and internal fixation. She was started on treatment 14 days after the onset of symptoms with chloromycetin and erythromycin. She also had an arthrotomy for drainage. This was packed open with vaseline gauze and a hip spica cast was applied. The patient also had arteriosclerotic heart disease, pulmonary congestion, and cholecystitis. Nine months later she was ambulatory, and had no pain, but there was a slight amount of drainage, and a Whitman type of osteotomy was planned.

Group IV

All patients in this group were treated as outlined above with both systemic and local antibiotics.

L. S. was a 15-year-old male with Staphylococcus aureus infection of the right knee. Treatment was initiated ten days after the onset of symptoms. Eleven months later the patient was asymptomatic, had a full range of motion and was considered normal radiographically.

T. B. was a 30-year-old male with Staphylococcus aureus infection in the knee. The patient had a history of trauma with subsequent locking and marked pain, and was considered to have a torn meniscus. At the time of arthrotomy pus was found. Four months later he had an effusion and neuroma in the operative scar. Aspiration at that time revealed clear fluid which was negative on culture. Six months after his infection he was reported to be in another hospital because of neuroma pain.

S. W. was a six-year-old female with infection in the knee, organism unknown. There was a history of having been struck on the knee previously. Treatment was started one day after the onset of symptoms. Thick pus was found at the time of arthrotomy. Four months later the patient was asymptomatic, had a full range of motion, and the sedimentation rate was 10. She did not return for follow-up observations.

C. L. was a 3-week-old female with Staphylococcus aureus infection of the left hip. The infant was premature and had a needle puncture of the hip joint in the course of a femoral venipuncture.

Subsequently she developed fever and marked irritability on moving. X-rays revealed dislocation of the hip with a distended capsule. Treatment was started 17 days after the onset of symptoms. Subsequently she had an unstable hip and open reduction was done. Fourteen months later there was evidence of active infection and she was maintained in a hip spica cast. Development of the femoral head was markedly retarded on X-ray.

C. M. was a 64-year-old male with Staphylococcus aureus infection of the knee and elbow. The patient had rheumathoid arthritis for six years and was on high doses of steroids. For 30 days he received 10,000,000 u of penicillin intravenously, and arthrotomy was done 90 days after onset of symptoms. The patient was thereafter cared for by his private physician and was lost to follow-up.

G. R. was a 1-month-old female with Staphylococcus aureus infection of the left knee. The patient had icterus of the newborn and high neo-natal fever. Five months later she was clinically normal but there was slight inequality of the epiphyses on X-ray.

R. R. was a 34-year-old male with Staphylococcus aureus infection of the left knee. Eighteen years previously he had a biopsy of the distal femur with the diagnosis of luetic periostitis. 80 cc of pus were removed at arthrotomy. Two years later he had some pain, intermittent drainage, and wore a long leg brace. X-rays showed destruction of all adjacent bony parts and amputation is being considered.

SUMMARY OF FOLLOW-UP

Group I 3 normal at 3 yrs., 3 yrs., and 6 mos.
1 luxating hip at 2 yrs.
2 no follow-up

Group II 2 normal at 16 and 18 mos.
1 residual joint destruction at 9 mos.
1 expired at 3 mos. with no active infection.

Group III 2 normal at 3 yrs. and 7 yrs.
1 drainage and limited motion at 21 mos.
1 expired

Group IV 3 normal at 4, 4, and 10 mos.
2 bony malformation in the joint at 9 mos. and 3 yrs.
1 neuroma formation
1 no follow-up

SUMMARY AND CONCLUSIONS

Twenty-one cases of acute pyogenic arthritis are presented. In this study males and females were equally affected as were all ages. It is felt that proper evaluation of end results can be made only if a standard method of treatment is employed as is being done with the technique outlined for Group IV.

No patients died of infection. All patients with adequate drainage had improvement of the acute process soon thereafter. Early definitive treatment seems to be the most important factor in obtaining a satisfactory long-term result.

At the present time it is recommended that suspect cases of acute pyogenic arthritis be considered emergencies in that destruction of the articular surfaces by pressure necrosis and proteolytic enzymes can be quite rapid. Such destroyed surfaces never return to normal. Local examination including measurements of circumference and area of erythema must be detailed. Cultures and laboratory studies should be done immediately, and treatment begun. Should fluctuation develop or the clinical picture worsen, surgical intervention must be considered.

REVIEW ARTICLE

ENDOCRINE ABLATIVE PROCEDURES IN THE TREATMENT OF DISSEMINATED BREAST CANCER

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INTRODUCTION

The rationale for oophorectomy for the control of metastatic cancer of the breast is based on the assumption that breast cancer grows more rapidly in a milieu containing estrogens and that by removing the main source of estrogens, tumor growth will be retarded. The major extragonadal source of estrogens is the adrenal gland; so logically adrenalectomy would appear to be the next step in the control of breast tumor growth. This reasoning is countered by the fact that added estrogen produces tumor regression in increasing frequency, the longer the time from the menopause. Also the incidence of breast cancer increases with age, being higher in patients well past the menopause at which time circulating estrogens are very low. Furthermore, patients who have responded favorably to estrogens or androgens previously are more apt to respond favorably to an adrenalectomy following a relapse from previous therapy. It is also well known that only a minority of patients have a favorable response to additive or ablative hormone therapy. Thus, favorable response in patients with breast cancer to hormone ablative procedures cannot be explained by the simple thesis of endogenous estrogen suppression. The mechanism of action of breast cancer suppression during hormonal alteration needs clarification, since the explanation of this phenomenon may throw light on the etiology of this most common cancer in the woman.

Studies of the excretion pattern of estradiol, estriol and estrone by Bulbrook *et al.*[1] have failed to clarify the picture. The work of Bulbrook *et al.*[2] on the urinary excretion pattern of 17-hydroxycorticosteroids and etiocholanolone, however, suggests that the ratio of certain steroids from the adrenal gland differs in patients who respond favorably to endocrine ablative procedures compared to those who do not.

Despite the confusion as to the mechanism by which suppression of ovarian function benefits patients with breast cancer, clinicians versed in the course of the disease are unanimously agreed that oophorectomy is the first systemic treatment to be undertaken in the control of progressive disseminated disease in the menstruant.

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Whether oophorectomy should be performed on a menstruant at the time of treatment of the primary cancer, the misnamed "prophylactic castration," is probably the most frequently asked question to the cancer specialist. No hormone additive or ablative procedure cures breast cancer; so the only possible benefit that could be expected from "prophylactic castration" is a delay in the clinical manifestation of metastases in some of those patients in whom the disease is not cured by mastectomy. In only 30% of those patients will this delay occur, as oophorectomy benefits only 30% of patients with disseminated breast cancer. Thus, of 100 menstruants castrated at the time of mastectomy, 40 will probably be cured by the mastectomy and will have been castrated needlessly, 60 will not be cured but in only 18 of these will castration produce a modest benefit and that benefit will be a delay in the appearance of clinically disseminated disease. In other words, 72 women will have the emotional impact of an artificial menopause unnecessarily superimposed on that caused by the loss of an important feminine appendage. The added fact that the tumor response to oophorectomy is one of the best guides for the proper selection of patients for either an adrenalectomy or hypophysectomy is another reason for withholding this procedure until clinically demonstrable disease is present, and the behavior of the tumor to oophorectomy can be determined.

As with any therapeutic procedure, the proper selection of patients is essential to obtain the maximum benefit from oophorectomy. The patient should have evidence of *progressing* disseminated cancer that cannot be adequately controlled by local radiation or surgery. She should show evidence of having active ovarian function by being a menstruant or within a year of her last period. It is extremely unlikely that a patient more than one year after the menopause will receive benefit from this procedure unless she experiences periodic breast engourgement, shows no evidence of breast atrophy, and/or has highly cornified vaginal exfoliative cytology. In the patient who has had hysterectomy and whose ovarian status is unknown, the decision as to the advisability of oophorectomy should be made on the basis of the clinical findings suggesting the status of ovarian activity.

As neither endocrine additive nor ablative procedures will cure breast cancer and the beneficial effects, when they occur, will last a limited time (from 3 months to 2 to 3 years as a rule) oophorectomy should be delayed until adequate control of the disease can no longer be accomplished by local means. Breast cancer, though disseminated, not infrequently remains in a clinically static state for fairly long periods of time while the patient feels well and is apparently living in "symbiosis" with her disease. A sudden alteration in the endocrine milieu at this time will be of no benefit and might even activate the disease. Oophorectomy should, therefore, not be done until evidence of worsening of the disease is present. On the other hand, delaying oophorectomy until the disease has progressed to a point when rehabilitation is very dubious, even if tumor suppression is accomplished, is to be condemned.

Although pleural effusion due to dissemination of the tumor is definite evidence of systemic manifestation of the disease, this particular finding may be the only evidence of disseminated disease for remarkably long periods of time. When this occurs it is frequently wiser to treat the effusion locally than to resort to systemic therapy such as oophorectomy. This can be done by the injection of chemotherapeutic agents into the pleural cavity, by the use of radioactive isotopes of colloidal gold or chromic phosphate, or by the surgical procedure of pleural stripping. If the predicted survival appears to be reasonably long, pleural stripping is preferable as this is not so apt to produce pocketing of fluid and contraction of the visceral pleura, a frequent late complication of intracavitary therapy.

Patients with discreet parenchymal lesions in the lung will not infrequently have a favorable regression, but patients with a lymphatic spread into the lung usually have a poor response. It is unusual for a patient with inflammatory lymphatic spread of the tumor on the chest wall, the so-called "inflammatory carcinoma," to respond favorably although other soft tissue lesions may dramatically recede. Patients with extensive visceral metastases very rarely respond favorably to endocrine ablative therapy. However, widespread osseous metastases do not preclude a good result if the bone marrow has not been too greatly replaced by tumor. In the retrospective study of the Joint Committee of the American College of Physicians and the American College of Surgeons,[3] menstruants under the age of 35 showed regression following oophorectomy in only 16% of the cases, while over the age of 35 menstruants showed a regression rate of 34%. Although this series was not large enough to be statistically significant, our own experience tends to confirm the impression that the young menstruant with breast cancer is not as apt to improve following an oophorectomy as is the older menstruant.

The evaluation of the patient who is to be considered for any endocrine ablative procedure requires an adequate metastatic survey to determine the extent of the disease. This should include as a minimum an X-ray of the skull, cervical, thoracic and lumbar spine, pelvis and upper portion of the femurs, and chest. In addition to complete hemogram and urinalysis, estimation of bromsulfalein retention, alkaline phosphatase and serum calcium should be included. Pulmonary function studies, electrocardiogram and bone marrow studies may be indicated in certain cases. These baseline studies are essential in order to have comparative data at a later date so that the results of therapy can be adequately determined.

Numerous studies as to the effectiveness of surgical oophorectomy have been published. The incidence of regression reported has varied from around 50% to 20% depending on the criteria used by the investigator. Using the criteria of regression of the Joint Committee of the American College of Physicians and the American College of Surgeons[4]: "evidence of regression of one or more lesions without the development of any new lesions or increase in size of any lesion at six months following oophorectomy", the incidence was 28%. Using the definition of regression of the Cooperative Breast Study Group of the Cancer Chemotherapy National Service Center of the U.S. Public Health Service[5]: "50% reduction of size of one or more dominant lesions without development of any new lesion or increase in the size of any previously present lesion", the incidence of regression in this prospective study was the same.

In general, the patient most apt to receive gratifying benefit from an oophorectomy is the woman over 35 years of age who is still a menstruant, who has mainly osseous or soft tissue disease, and has had a long interval from the diagnosis of the primary disease to clinical evidence of metastases.

There has been no carefully randomized series to compare surgical oophorectomy with X-ray castration. It is possible that the latter is as effective when proper dose to the ovary has been given. However, until such a study has been undertaken I feel the surest method of removing ovarian hormone secretion is extirpation.

Adrenalectomy as a treatment for disseminated breast cancer has been selectively used in certain centers since the first report by Huggins and Dao in 1951.[6] Initially only very far advanced cases were selected and the incidence of failures was so high that many centers discouraged its use in palliation. It has only been after many years of experience that a proper selection of clinical material has demonstrated the efficacy of this procedure. Olivecrona and Luft[7] reported on the use of hypophysectomy as an alternative to adrenalectomy for palliation in breast cancer in 1954. It appeared from this work and that of

Pearson *et al.*[8] that hypophysectomy could be done with less morbidity and mortality than adrenalectomy and with improved regression rate. However, recent retrospective studies by the Joint Committee of the American College of Physicians and the American College of Surgeons[3,4] showed no difference in regression rate between adrenalectomy and hypophysectomy. Survival, surgical morbidity and mortality were also the same. A random study in England,[9] also showed the effectiveness of these two not to be statistically different.

Whether adrenalectomy or hypophysectomy should be selected for a patient depends in part on the availability of the proper surgeon. Obviously many more surgeons are available for adrenalectomy than for hypophysectomy. Patients with tumors in certain sites might have one or the other procedure to advantage. For example, in a patient with considerable abdominal metastases it might be technically more feasible to employ hypophysectomy because of possible difficulty in exposing the adrenal gland. A patient with metastases in the skull might present a problem to the neurosurgeon. A patient with respiratory impairment due to pulmonary metastases might withstand hypophysectomy better than adrenalectomy.

It is essential that every means be used in prognosticating the results of adrenalectomy or hypophysectomy as these are formidable surgical procedures even though the mortality rate should be low. Also these procedures so alter the patient's hormonal balance that she will require careful medical supervision the rest of her life. Although the overall regression rate following either of these major endocrine ablative procedures in a large series[4] is only about 30% this includes many cases who would not be selected for this procedure today, as experience has shown its futility in certain patients. It has been from these earlier experiences, however, that conclusions can now be drawn as to the type of patient on whom adrenalectomy should produce worthwhile palliation and the type in whom the chance of improvement is low.

It is probable that by proper selection of patients, worthwhile palliation of disseminated breast cancer can be obtained in 60% to 70% of the cases following adrenalectomy or hypophysectomy. For example, if careful follow-up of the menstruant who has been castrated because of metastatic cancer demonstrates that the patient has had an objective regression of tumor, this factor alone will give her nearly a 50% chance of a favorable response following adrenalectomy or hypophysectomy. Furthermore, if the period from mastectomy to clinical evidence of metastases, the "free interval," is 3 years or over, the chance of regression following adrenalectomy is greatly increased. In one series the mean time of "free interval" was 38.6 months in those experiencing a regression following a major endocrine ablative procedure and 30.6 months for those not showing a regression ($P < .01$). If the patient has mainly osseous or soft tissue disease the chance of adrenalectomy producing regression is twice as great as if the metastases are predominantly visceral.Thus the patient, the most likely to benefit from adrenalectomy or hypophysectomy, is one who has had a long cancer "free interval" following mastectomy, has mainly osseous or soft tissue disease and has had a favorable response following therapeutic castration. The patient with a short "free interval," with a history of no regression of tumor following oophorectomy, and with visceral metastases, runs a very poor chance of receiving palliation. Postmenopausal patients who developed primary cancer of the breast before the menopause, then went through the menopause without signs of metastases and did not develop metastases until considerably later, also showed in the above series a relatively high incidence of regression.

As mentioned above, a pre-operative evaluation of the extent of the disease before a major ablative procedure is undertaken is essential, not only to make evaluation of therapy possible, but as a

guide to further treatment.

The pre-operative management in major endocrine ablative surgery is started the night preceding surgery. Cortisone acetate is given intramuscularly in doses of 50 mgm. every 6 hours so there will be a depot of cortisone available during surgery in case a defect in the intravenous flow of hydrocortisone occurs. During the entire surgical period, 100 mgm. of hydrocortisone in 1000 ml of physiologic saline solution is administered by slow drip intravenously at the rate of about 20 drops per mintue. In the post-operative period adequate fluids are administered as with any post-operative patient and 50 mgm. of cortisone acetate is given intramuscularly every 4 hours for 4 doses, then every 6 hours for 4 doses and every 8 hours thereafter. If any signs of adrenal insufficiency develop, hydrocortisone should be added to the intravenous solution. If during the post-operative course of a patient who has been on the above regimen of replacement therapy, shock, hypotension or tachycardia develop, an investigation of causes other than adrenal insufficiency must be made as it is very unusual for the latter to develop if the above doses of corticosteroid are maintained. On the other hand, it is wiser to give added cortisone unnecessarily than to give an insufficient amount.

The dose of cortisone can be gradually decreased as the patient improves. Oral administration may be substituted for the injections as soon as the patient is able to retain feedings. The daily dose must be divided so that no longer than 8 hours elapses between doses as most all cortisone is conjugated or excreted after that period of time. Most patients can be discharged on a daily dose of 75 mgm. of cortisone acetate and after a few days may be able to reduce the dose to 50 mgm. as a maintenance. The dose must be raised if any stressful situation, such as excess fatigue, infection, diarrhea or fever intervenes. If the weather is hot or if the patient perspires freely for any reason extra salt, either in food or as tablets, should be taken. Very rarely 9-alpha fluorohydrocortisone in a dose of 0.1. mgm by mouth daily or 2 to 3 times a week may be necessary to maintain the serum sodium at a normal level. The patient and her attending physician are given written instructions on how to handle adrenal insufficiency including the use of intramuscular cortisone should nausea or vomiting preclude the usual oral dose. The patient is instructed to have a bottle of cortisone acetate suspension for intramuscular injection available, so it can be administered by a nurse or local physician if the necessity arises. With these precautions the incidence of severe adrenal insufficiency is negligible and patients well instructed in their management need not be followed medically any more frequently than would be indicated because of the disseminated cancer, once the maintenance daily dose of cortisone is established.

When reactivation of the disease occurs these patients usually require more than the usual 50 mgm. a day dose of cortisone because of the stressful effect of complications associated with deterioration. Rarely do added androgens or estrogens produce another regression in these patients but a trial of chemotherapy produces some palliation at times. It must be emphasized, however, that unless the dose of cortisone is increased considerably from the usual maintenance dose, adrenal insufficiency is often precipitated by the giving of a chemotherapeutic agent.

Although Lemon[1] claims that in his hands oophorectomized patients with breast cancer do as well on small doses of prednisone as they would following adrenalectomy or hypophysectomy, we have found regression in only 8% of patients given prednisone following oophorectomy compared with 30% following adrenalectomy or hypophysectomy. Dao[11] in a randomized study of 39 patients (20 treated with cortisone alone and 19 with adrenalectomy) experienced 44.5% obvious benefits in the adrenalectomized patients and none in the cortisone treated patients. In a similar randomized study of adrenalectomy

versus testosterone propionate[12] objective tumor regression was demonstrable in 23 of the 47 adrenalectomized patients and 9 of the 44 androgen treated cases.

Most investigators feel that administered corticosteroids cannot produce adrenal cortical suppression sufficient to achieve worthwhile tumor regression and that the known palliative effects of corticosteroids are being fallaciously interpreted as actual tumor regression.

SUMMARY

Oophorectomy should be the first systemic therapy for the treatment of advancing disseminated breast cancer. There is no evidence that this procedure will produce a higher incidence of total salvage if it is performed at the time of mastectomy than if used as a therapeutic procedure when metastatic disease becomes manifest. The patient's response to this procedure gives the therapist valuable prognostic information as to the efficacy of further sequential therapies.

Bilateral adrenalectomy or hypophysectomy as a therapeutic measure are worthwhile procedures for the palliation of breast cancer in patients falling within the guidelines outlined in this paper.

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ABSTRACTS AND REVIEWS

OF PUBLICATIONS BY THE STAFF

Histologic Changes in the Trachea Following Laryngectomy. T. E. Griffith and S. A. Friedberg: *Ann. Otol. Rhinol. & Laryng. 73:883-893 (Dec.) 1964.*

Changes in the mucosa of the trachea were observed at varying periods of time following laryngectomy. Tissue from the tracheal bifurcation was obtained through a bronchoscope passed into the permanent tracheostomas of laryngectomized patients. An increased incidence of tracheal epithelial metaplasia was observed in ten of the twelve patients studied and in all twelve instances metaplasia of the basal layer was present.

All of the patients in this series had been heavy smokers and chronic inflammatory changes in the tracheal mucosa were apparent. In two patients the epithelial changes were considered to be compatible with intraepithelial neoplasia or so-called carcinoma-in-situ.

The cause of the mucosal changes is unknown. It is possible that the increased incidence of metaplasia may be due to change in air currents resulting from tracheostomy, to aspiration techniques, smoking or exposure to environmental pollution.

Treatment of Complications of Gastroduodenal "Steroid Ulcers." D. L. Roseman, S. G. Economou: *Archives of Surgery 90, 488-494, April 1965.*

Patients with steroid ulcers present and behave differently than patients with ordinary ulcers.

Complications of steroid ulcers are much more serious in patients with malignant disease. In fact, every patient with a bleeding or perforated steroid ulcer that was being treated for malignant disease died.

Steroid ulcers often perforate silently—any patient on steroid therapy that complains of vague chest pain or abdominal pain should have an immediate upright x-ray of the diaphragms in search of pneumoperitoneum.

The operation of choice is the simplest one that will control the acute complication. These patients should, in general, be operated upon as soon as the diagnosis of perforation or hemorrhage is made.

Formic Acid Corrosion for the Demonstration of Pulmonary Elastic Tissue. R. W. Carton, and J. Dainauskas: *Stain Technology, Vol. 39:5:317, September, 1964.*

By a revised technique, human pulmonary elastic tissue can be isolated in a form suitable for examination under the stereoscopic microscope. Fresh human lungs from autopsy are fixed by intrabronchial infusion with 10% formalin for 24 hr. Slabs 1.5 cm thick are cut and the formalin removed in running water. One such slab is embedded under intermittent vacuum in an aquaeous mixture containing 15% gelatin, 10% glycerol, and 1% phenol; then allowed to gel. Frozen sections 2 mm thick are cut on a large-section MSE sledge microtome. Squares 3 x 3 cm from such a section are corroded for 4-5 days in 88% formic acid at 45°C, washed once with distilled water, and mounted in glychrogel containing 6% gelatin. The elastic tissue network of the lung will have been freed from surrounding elements. The preparation should be stored in a refrigerator. Blocks for thin sections and large thick uncorroded sections can be prepared from the same lung as part of an over-all procedure.

Renal Hypothermia. D. G. A. Eadie, N. L. Tilney, H. Najafi, S. G. Economou, and E. J. Beattie, Jr. *Archives of Surgery 90, 554-560, April, 1965.*

A method of transarterial perfusion to the solitary kidney was described.

Results show that this method may be satisfactorily used to induce renal hypothermia.

A mean temperature of 21 C gives adequate protection to the canine kidney against two hours of total ischemia.

No injury was caused to the renal morphology by inducing hypothermia by this method.

Attack on Nucleoprotein in Cancer Therapy. F. E. Knock: *J. Am. Geriatrics Soc., Vol. 13, 313-323, 1965.*

Because sulfhydryl-containing residual protein bound to DNA is as indispensable for maintaining chromosome structure as is DNA itself and because sulfhydryl inhibitors preferentially attack cancer cells, sulfhydryl inhibitors have been investigated for clinical cancer chemotherapy. The sulfhydryl inhibitor oxophenarsine with adjuncts fluoride, malonate and heparin has effected objective regression in the majority of patients whose tumor response could be measured objectively. In vitro agar plate assays used to select chemotherapy for each patient have predicted known sensitivities of animal tumors and results of clinical cancer chemotherapy with sulfhydryl inhibitors and many other drugs.

The sulfhydryl inhibitor oxophenarsine contains arsenic. New iodoacyl and maleimide sulfhydryl inhibitors free of arsenic show activities equalling or exceeding that of oxophenarsine against many human solid tumors in vitro. Clinical application of arsenic-free sulfhydryl inhibitors has been started for patients with tumors sensitive to the drugs by preliminary agar plate assay and for whom the new sulfhydryl inhibitors are the most active drugs available. The iodoacetyl compound SI-1 (SQ 17644, 2-(N4-acetylsulfanilamido) ethyl iodoacetate) has shown promising results in the first six cancer patients treated with the new drug.

Sympathetic Reflex Dystrophy. G. de Takats: *The Med. Clinics of N. America, 49:1, January 1965.*

Reflex dystrophy, a minor causalgic state, is fairly well known to surgeons and orthopedists engaged in caring for traumatized patients. Both in war and in peace, as a result of the large accident rate, a certain percentage of patients, estimated to be 5 to 15 per cent of the total of those injured, suffer from minor or significant forms of this neurovascular disorder. The internist, however, sees it principally in patients with joint, tendon and vascular lesions; for example, the shoulder-hand syndrome after coronary occlusion and after hemiplegia. While he may employ heat, physical therapy, massage, local and systemic steroids, narcotics and psychotherapy, the point has been made that early adequate interruption of sympathetic efferent pathways, first by intermittent blocks, or if indicated by sympathectomy, specifically relieves the phenomenon. Three stages of reflex dystrophy are described, each one becoming more intractable with the course of time.

Smoking Withdrawal: The Physician's Role. G. de Takats, M.D.: *The Illinois Medical Journal, 127:2, 141-146, Feb. 1965.*

The majority of physicians have expressed their belief that smoking is hazardous to health. There has been, however, neither a sizable individual nor an organized attempt to transmit and implement this belief to the public. While mass media are beginning to inform the population about the pro's and con's of tobacco consumption, the majority of physicians, with some notable exceptions, have taken an indifferent attitude; some have even taken a cue from industry and speak about curtailing the freedom of the consumer. The duty of the medical profession as a whole and as individuals, is to inform the smoker about what he is doing to himself and to his family. The increased morbidity of the smoker is putting an increased burden on his community and indirectly on the whole country.

Chemotherapy of Gastrointestinal Cancer. N. L. Tilney and S. G. Economou: *Geriatrics, 265-276, April 1965.*

Much effort has been expended in the pursuit of effective chemotherapeutic drugs for gastrointestinal cancer. Despite many advances in surgical and postoperative techniques for cancer in the past years, long-term cure rates are not improving as rapidly as hoped. As yet no chemotherapeutic agent has been found to give truly effective and lasting remission of the disease. Many drugs, routes of administration, and dosages for these drugs are being tried clinically at this time in attempts to discover combinations of factors that will make more successful the chemotherapy of gastrointestinal cancer.

Simplified Method for Fluorescent Antibody Staining of Tissue Cultures. F. Deinhardt and R. E. Dedmon: *Nature, 205:4976, pp. 1122-1123, March 1965.*

A simplified method for fluorescent antibody staining of tissue culture preparations with the aid of a special slide support rack and a staining chamber both developed in the Department of Microbiology, Presbyterian-St. Luke's Hospital is described.

Tracheostomy in the Newborn. P. H. Holinger, W. T. Brown and D. G. Maurizi: *American Journal of Surgery, Vol. 109, 771-779 (June 1965).*

Infants requiring tracheostomy in their first year of life present significant differences from older children in indications, management and prognosis. A review of technic and an analysis of the problems of tracheostomy peculiar to infants in their first year of life are presented. The series of sixty-two cases reported in 1953 and the series of eighty-six cases seen from 1954 to 1963 inclusive are compared.

It is apparent that (1) the incidence of tracheostomy in infants under one year of age is increasing due to a broadening of indications, greater acceptance of tracheostomy as an adjunct to other therapy, and a lower morbidity rate for the operation itself through improved surgical technics and post-operative care. (2) The downward trend in the incidence of inflammatory processes continues, while the number of tracheostomies performed for or during the management of congenital anomalies continues to rise more rapidly than the former is decreasing. (3) Further analysis shows that infants in the more recent series were tracheotomized at an average age considerably younger than those in the earlier series. (4) An analysis of the twenty-seven infant deaths in the more recent series shows the death rate to vary according to and be dependent upon the underlying defect necessitating tracheostomy. (5) The difference in the death rate between the two series is statistically insignificant.

The Human Urinary Bladder Mucosa. H. Battifora, R. Eisenstein, and J. H. McDonald: *Investig. Urology. Vol. 1, No. 4, 354-361, January, 1964.*

The mucosa of the human urinary bladder, as studied with the electron microscope, has the same general structure as the bladder mucosa of other mammals. There are numerous pinocytic vesicles, cytoplasmic vesicles, and intercellular spaces with a structural relationship supplying morphologic evidence of extensive transport of water and solutes.

These cells are simple in structure and, therefore, may be especially suitable for an electron microscopic study of changes which accompany the transitions characterizing the various stages of neoplasia.

Descriptions of the structure of the urinary bladder mucosa, as studied with the electron microscope, are available for several vertebrates including the mouse (1), rat (2) and some amphibians (3). During the course of an electron microscopic and biochemical study of human bladder neoplasms, we have examined bladder mucosal biopsies, several of which have been from patients without bladder disease. We have found that there are differences between the structure of the normal human bladder mucosa and that described for other vertebrates.

Hypertonic Urea in Experimental Cerebral Edema. A. R. Clasen, P. Cooke, S. Pandolfi, G. Carnecki and G. Bryar, M.D.: *Archives of Neurology, Vol. 12, 424-434, April 1965.*

Focal areas of hemorrhagic necrosis were produced in brains of anesthetized monkeys. This resulted in a sustained increased intracranial pressure. This pressure was reduced by intravenous hypertonic glucose given six hours after injury. The brains were removed and the hemispheres analyzed for water and electrolytes. The damaged hemisphere showed an increase in weight, water, sodium, chloride, and calcium. These changes were in excess of those predicted from the degree of hemorrhage as estimated by the increase in the iron content of the hemisphere. There was a direct correlation between the weight increase of the damaged hemisphere and the extent of damage. No evidence that this form of therapy reduced the cerebral edema associated with the lesions was found, the decrease in pressure being the result of dehydration of the undamaged hemisphere. The data further indicated that water was removed from this hemisphere without a concomitant decrease in tissue chloride.

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ETIOLOGY, DIAGNOSIS, AND MANAGEMENT OF GLAUCOMA IN ADULTS

EDWARD A. PUSHKIN, M.D.[1]

Glaucoma may be defined as an increase of intraocular pressure or ocular tension which is incompatible with normal functioning of the eye. Vision is irreversibly damaged by atrophy of the optic nerve. Accordingly, the clinical problem lies in the detection of glaucoma by all physicians, and prevention of visual loss through proper medical or surgical treatment by ophthalmologists.

One of every eight blind Americans is blind because of glaucoma, and many more have lost the sight of one eye from this cause. Every year, glaucoma brings blindness to 3,500 more people in the United States, due primarily to lack of detection in the early stages and to a less extent to unsuccessful treatment. Surveys in many parts of the world have established that at least one of every 50 individuals over 40 years of age has undiagnosed glaucoma; or that 800,000 individuals in the United States are losing their vision unknowingly from glaucoma. Because the most common form of glaucoma is transmitted as a recessive hereditary characteristic, 12-15% of individuals in families with glaucoma are affected.

Excluding glaucoma secondary to other ocular disease such as iritis, probably not more than 10% of the cases of primary glaucoma develop dramatic symptoms of acute congestion of the eye, severe pain, and rapid loss of vision. Another 20% may have vague symptoms of blurred or foggy vision which is not corrected by frequent changes of glasses, difficulty seeing in the dark, iridescent vision or rainbow-colored rings around lights, or mild aching of the eyes. The remaining 70% of the patients with primary glaucoma have no symptoms whatsoever until extensive damage to the optic nerve produces loss of side vision or the patient accidentally covers one eye to discover that the other eye is blind. This type of glaucoma, the so-called open angle glaucoma or chronic simple glaucoma, has been described as a "thief in the night" which usually occurs in individuals over 40 years of age.

CIRCULATION OF AQUEOUS

A brief review of the formation, circulation, and drainage of aqueous in the anterior segment of the eye is of value in understanding the etiology and rationale for treatment of glaucoma (Fig. 1). Aqueous is formed from the ciliary processes, partly as an active secretory process perhaps involving pinocytosis, and partly by simple filtration across the blood-aqueous barrier involving osmotic forces. The enzyme, carbonic anhydrase, is necessary for part of the aqueous secretion, as evidenced by inhibition of aqueous formation about 50% by carbonic anhydrase inhibitors such as Diamox (acetazolamide), Daranide (dichlorphenamide), Neptazane (methazolamide), or Cardrase (ethoxzolamide). These substances are therefore useful when given orally in the medical treatment of glaucoma, reducing the ocular tension by reduction in the formation of aqueous. Diuril, which is also a diuretic similar to Diamox, does not reduce aqueous formation because it has no specific effect on carbonic anhydrase in the ciliary processes. Recently, electron microscope studies have

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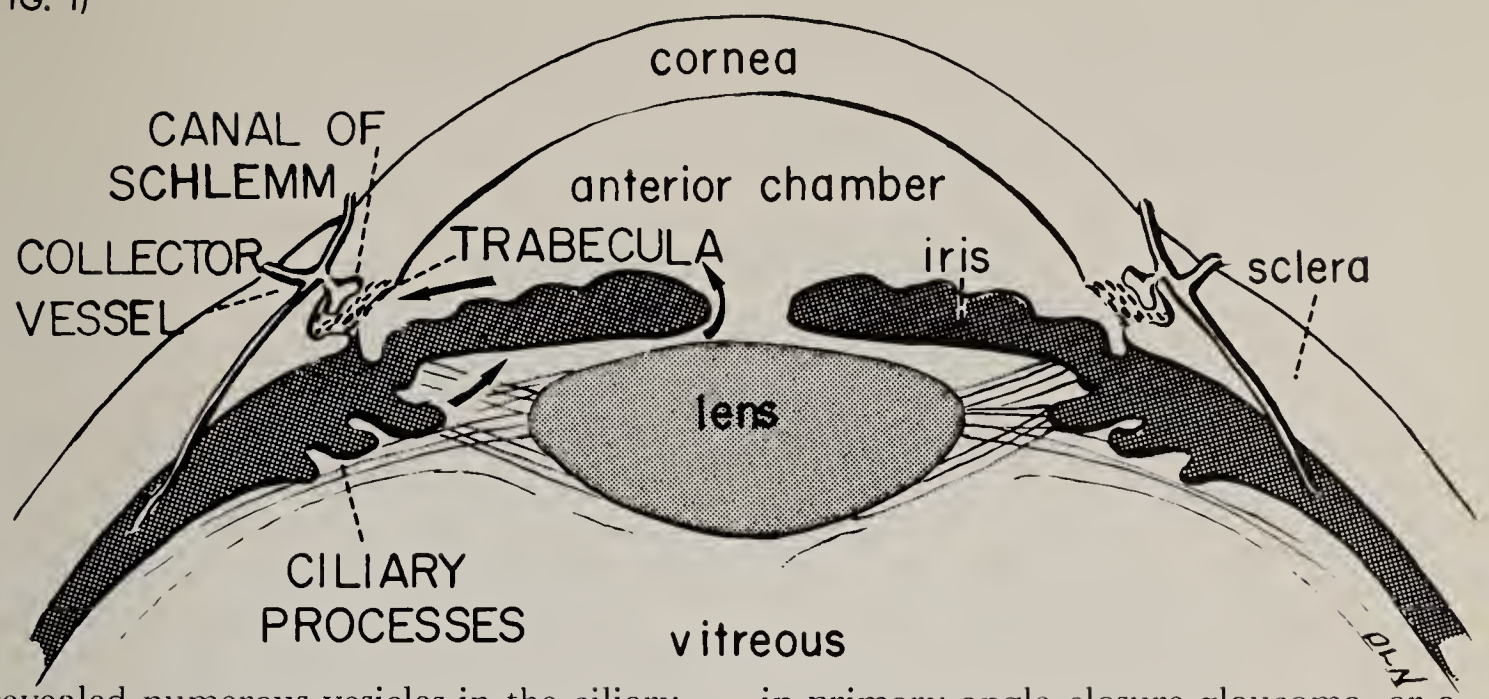
CIRCULATION OF AQUEOUS

(FIG. 1)

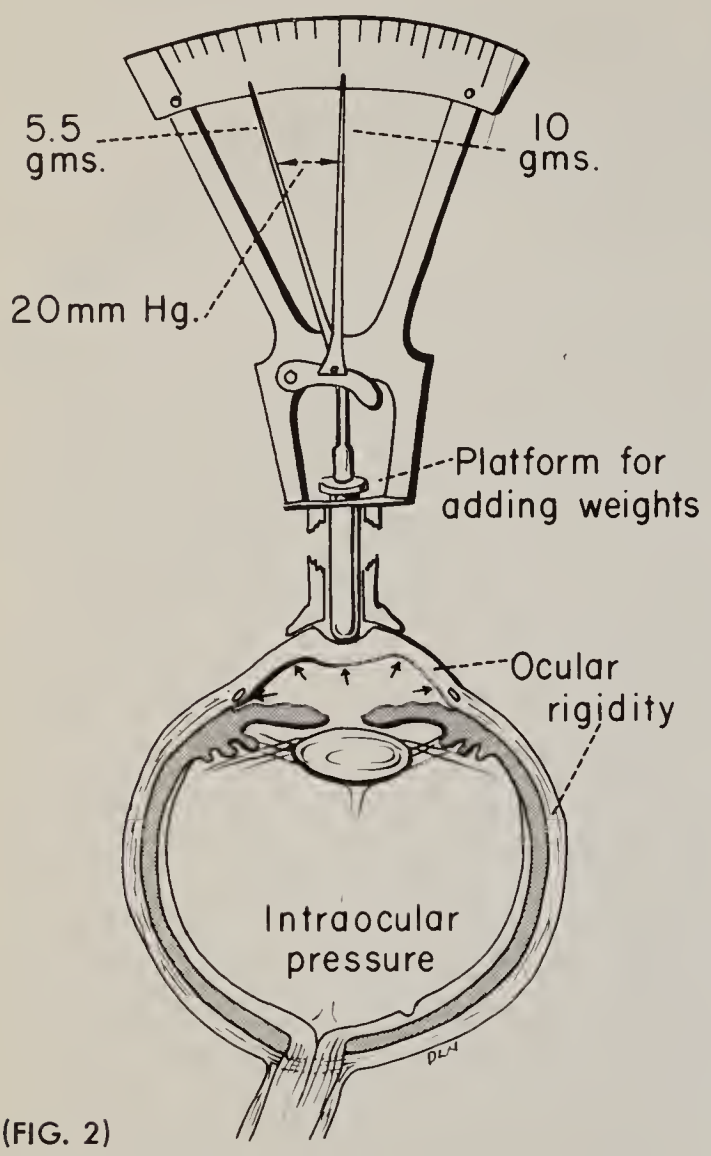


revealed numerous vesicles in the ciliary epithelium which have been postulated as a means of water transport from blood to aqueous (pinocytosis or "cell-drinking"). The number of such vesicles increases after the use of Diamox. By some unknown mechanism, local instillation of 1% or 2% epinephrine also reduces the formation of aqueous about 30% in addition to the effect produced by Diamox. In older individuals, the rate of aqueous secretion diminishes, and this helps compensate for the normal reduction in the drainage of aqueous with increasing age. The aqueous itself is osmotically hypertonic to the blood plasma, thus inducing filtration from the blood. The aqueous flows between the iris and lens into the anterior chamber, thence through pores in the trabeculum into the canal of Schlemm. Either a physiologic block as in primary angle-closure glaucoma, or a pathologic block from posterior adhesions (synechias) of the iris to the lens following critis can produce a forward bulging of the iris ("iris bombe") and secondary glaucoma. If the root of the iris should be pushed forward to block the entrance to the trabeculum mechanically, the so-called angle-closure or congestive glaucoma develops. Resistance to outflow of aqueous through the trabeculum is the cause of elevated intraocular pressure found in open angle glaucoma. After passing through the trabeculum, the aqueous enters the canal of Schlemm, which is like an enlarged capillary in the sclera just outside the periphery of the cornea. From this point, aqueous drains into the "aqueous veins" and collector vessels in the sclera which then enter the general venous circulation.

OPEN ANGLE GLAUCOMA

Diagnosis. The early diagnosis of open angle glaucoma is made by detection of increased ocular tension or intraocular pressure in the eye. Ocular tension consists of intraocular pressure, modified by rigidity of the corneo-scleral coat and intraocular vascular channels. Tension is commonly measured with the Schioetz tonometer (Fig. 2). After instillation of a local anesthetic such as ½% Ophthaine (proparacaine) or ½% tetracaine, the footplate of the tonometer is placed directly on the patient's cornea. The plunger indents the cornea, more indentation occurring if either the intraocular pressure or ocular rigidity is low. This produces a higher reading on the instrument scale which has been correlated experimentally with the intraocular pressure of enucleated eyes. Ordinarily, the ocular rigidity is normal and so this method gives a reliable measurement of the intraocular pressure. The weight of the plunger system is 5.5 grams, and a scale reading of 4 units indicates the upper limit of average normal tension

(i.e., 20 mm. Hg.). A reading below 4 scale units indicates probable glaucoma, which should be confirmed by the ophthalmologist with other tests outlined briefly below before instituting a lifetime of glaucoma treatment. The so-called finger tension, taken by palpation through the upper eyelid, is quite unreliable.

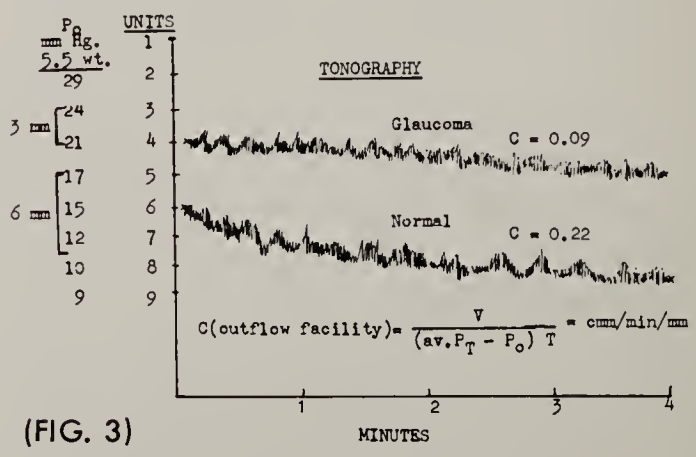


(FIG. 2)

Because at least 2% of the population over 40 years of age have undiagnosed glaucoma and many of these individuals do not regularly come under the care of eye specialists, routine estimation of the ocular tension with the Schioetz tonometer should be performed by the practicing physician during routine physical examination on these patients. In rare cases, the ocular rigidity may be abnormal and therefore an erroneous estimation of the intraocular pressure by the Schioetz tonometer might be obtained; e.g. a low scleral rigidy and erroneously low estimation of intraocular pressure by the Schioetz tonometer in myopia, thyroid exophthalmos and a few other conditions.

The Goldmann applanation tonometer can be used by the ophthalmologist to more directly estimate the intraocular pressure. The principle of this instrument is to determine the force necessary to make a small area of contact of the instrument with the cornea. Because the indentation of the cornea is very slight, ocular rigidity becomes an insignificant factor.

In cases of early open angle glaucoma, a single estimation of ocular tension or tonometry may be inconclusive. The intraocular pressure normally fluctuates during the 24 hours, usually being highest in the morning before arising, and this diurnal variation is greater in individuals with glaucoma. Because of the difficulty in taking tensions frequently during the entire 24 hours, the water provocative test has been devised. A liter of water is consumed within 5 minutes on an empty stomach, and tensions are recorded prior to the test and at 15 minute intervals for the next hour. Decrease in osmotic pressure of the blood induced by this test increases the rate of formation of aqueous. An individual with a normally filtering trabeculum will be able to take care of this added load, and the ocular tension does not rise more than 8 mm. during the hour following the water drinking. Although a rise in tension over 8 mm. is considered abnormal, about a third of early glaucomas have false negative values probably due to variations in the absorption of ingested water.

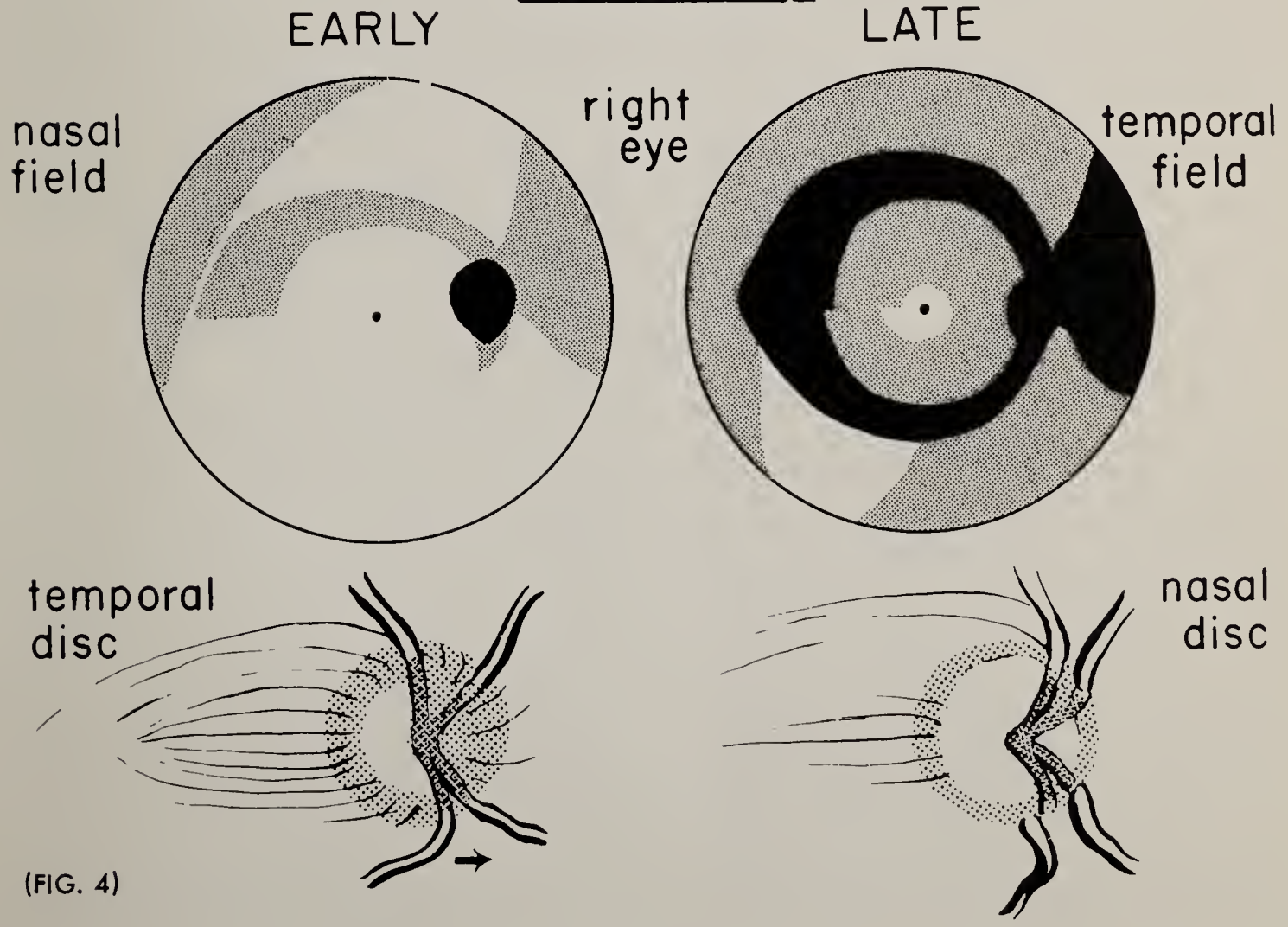


(FIG. 3)

Another method to determine the ability of the trabeculum to drain off aqueous is called "tonography". In this examination, the intraocular pressure is

artificially raised by placing an electronic modification of a Schioetz tonometer on the eye for four minutes, and the gradual reduction in tension is recorded mechanically, giving an index of the facility of outflow of aqueous through the trabeculum (Fig. 3). In a patient with glaucoma, the tracing is relatively flat with a calculated outflow of $C = < 0.13$, indicating an increased resistance to outflow. A normal drop in pressure indicates that the trabeculum is able to filter off increased amounts of aqueous when the intraocular pressure is artificially raised by the tonometer, or $C = 0.18$ or more. A combination of the water provocative test and tonography is the most effective method of diagnosing the earliest cases of glaucoma with only about 10% false negatives, a ratio of initial pressure outflow facility (Po/C) = over 100.

If the intraocular pressure remains elevated over the course of many months or even years, peripheral or side vision is destroyed first. The extreme importance of this side vision is recognized by the Department of Internal Revenue which allows deduction for blindness with a visual field which extends peripherally 20° or less. Visual field defects as determined on the tangent screen or other testing device are fairly characteristic for glaucoma (Fig. 4). The first change is an enlargement of the blind spot (position of the optic nerve), both temporally and in an arcuate form either above or below or both. This is caused by loss of retinal nerve fibers entering the optic disc which produces enlargement of the optic cup, increased pallor of the disc, and nasal displacement of the retinal vessels. The cause of this glaucomatous optic atrophy is uncertain. It may be due to a direct pressure necrosis of the nerve fibers. More likely, it is an atrophy of the nerve fibers secondary to ischemic necrosis, the smaller nutrient vessels to the disc being compressed by the increased intraocular pressure. It is interesting that individuals with systemic hypertension may show a greater resistance to optic nerve damage from glaucoma than a normal individual,



(FIG. 4)

and some care must be taken to keep the intraocular pressure low when the hypertensive patient is treated medically to reduce the blood pressure.

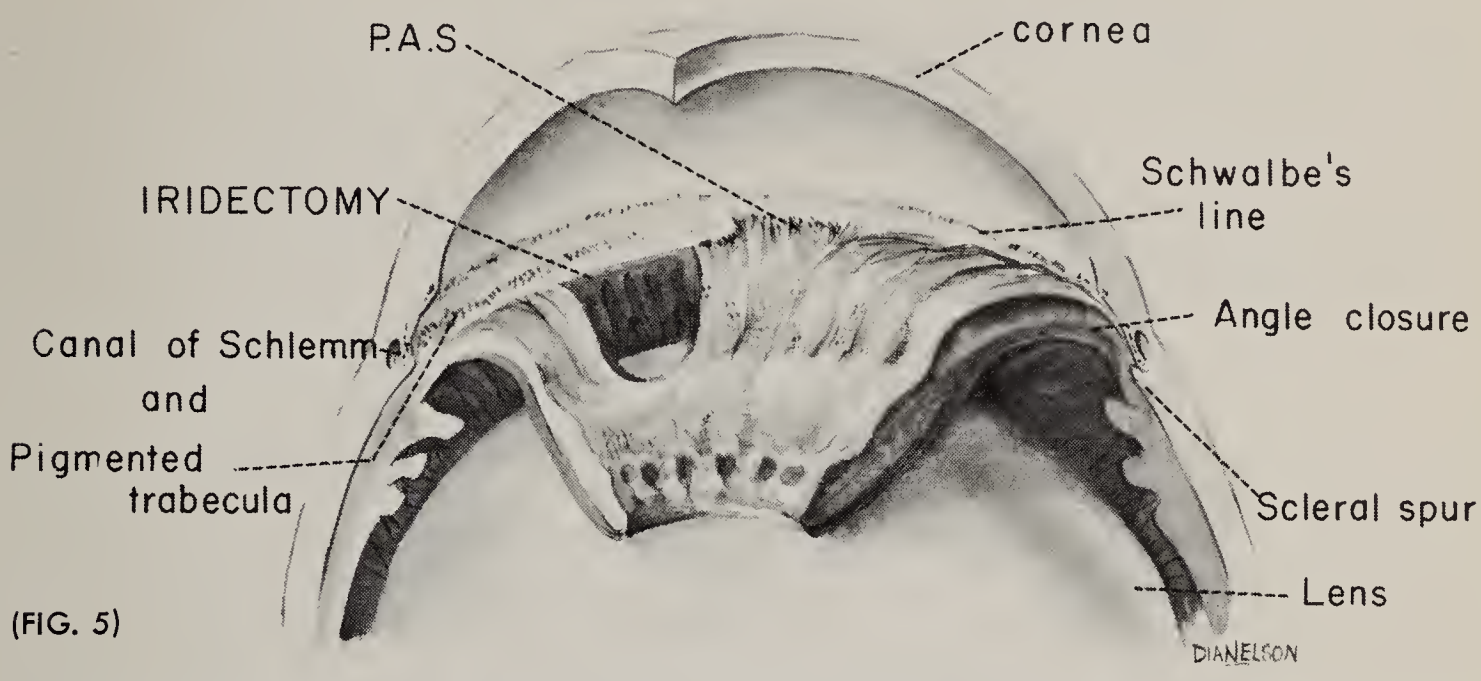
Management of Open Angle Glaucoma. To prevent glaucomatous optic atrophy and irreversible loss of vision, the ophthalmologist endeavors to maintain the intraocular pressure below 20 or at a level which does not result in further damage. This is accomplished either by reducing the inflow of aqueous or by increasing the outflow. Treatment is usually begun using various parasympathetic-omimetic drugs which act as miotics to constrict the pupil: (1) usually pilocarpine; (2) in more resistant cases, cholinesterase inhibitors such as physostigmine (Eserine) or prostigmine; and (3) in cases requiring long-acting, powerful miosis, such irreversible cholinesterase inhibitors such as Phospholine Iodide (echothiophate), Humersol (demecarium bromide), or Floropryl (isoflurophate). The means by which these miotics reduce the intraocular pressure is uncertain, but they probably open up the drainage spaces in the trabeculum and may have some vascular effects. Instillation of strong 1 or 2% solutions of epinephrine into the eye also improves the outflow of aqueous. If these agents are ineffective in normalizing the ocular tension, then a carbonic anhydrase inhibitor such as Diamox is usually prescribed systemically to reduce the formation of aqueous. If the intraocular pressure cannot be normalized by such medical treatment or if the visual fields continue to show further deterioration, operation is usually indicated. Most frequently, this consists of a filtering operation, in which a drainage pathway is created between the anterior chamber and the subconjunctival space. This bypass around the normal filtration channels allows aqueous to be drained from the eye by evaporation through the conjunctiva and absorption into the surrounding vessels. Because the success of such operations in only 75-90% and and because they are associated with some complications such as late development of cataract, such surgical methods to reduce the intraocular pressure are reserved as a last resort when medical management fails. Cyclodiathermy, or cauterization of the ciliary body to reduce formation of aqueous, is usually reserved for desperate cases in which other medical and surgical procedures have failed. Cryosurgical treatment involving freezing of the ciliary body is less reliable.

The question often arises whether belladonna or related compounds such as atropine or scopolamine can be used in patients with glaucoma. In this type of open angle glaucoma, where there is adequate space between the root of the iris and the trabeculum, such drugs can be used not only systemically, but mydriatics can be used locally in the eye to dilate the pupil without fear of aggravating the glaucoma.

ANGLE CLOSURE GLAUCOMA

This type of congestive glaucoma occurs in those eyes in which there is relatively little space between the root of the iris and the trabeculum; e.g., in hyperopic or far-sighted eyes or when the anterior chamber becomes more shallow with increasing age. A physiologic obstruction to the normal flow of aqueous from the posterior chamber between the iris and the lens into the anterior chamber develops, resulting in a forward protrusion of the iris (iris bombe) with mechanical closure of the trabeculum by the root of the iris (Fig. 5). This potential or actual blockage of the drainage angle can be observed through a special contact glass which permits observation of the trabecular area (gonioscopy). The closure of the angle by the root of the iris is precipitated by anything which causes dilatation of the pupil in such a predisposed eye; e.g., dilatation of the pupil for refraction or examination of the fundus, systemic use of atropine-like drugs, local instillation of epinephrine or even emotional stress with systemic mobilization of epinephrine, or even being in a darkened room such as when attend-

ing a theater. With the rather rapid increase of intraocular pressure induced by such mechanical blockage to the outflow of aqueous, symptoms develop: viz., (1) pain which may vary from mild aching to a severe pain associated with nausea and vomiting; (2) blurring of vision varying from brief episodes to almost complete loss of vision; (3) iridescent vision or rainbow type halos around lights, because edema of the corneal epithelium produces a prismatic refraction of light into a color spectrum; and (4) in acute and severe instances, the eye becomes very congested and the pupil becomes dilated, completing the classic signs and symptoms of acute congestive or angle closure glaucoma.



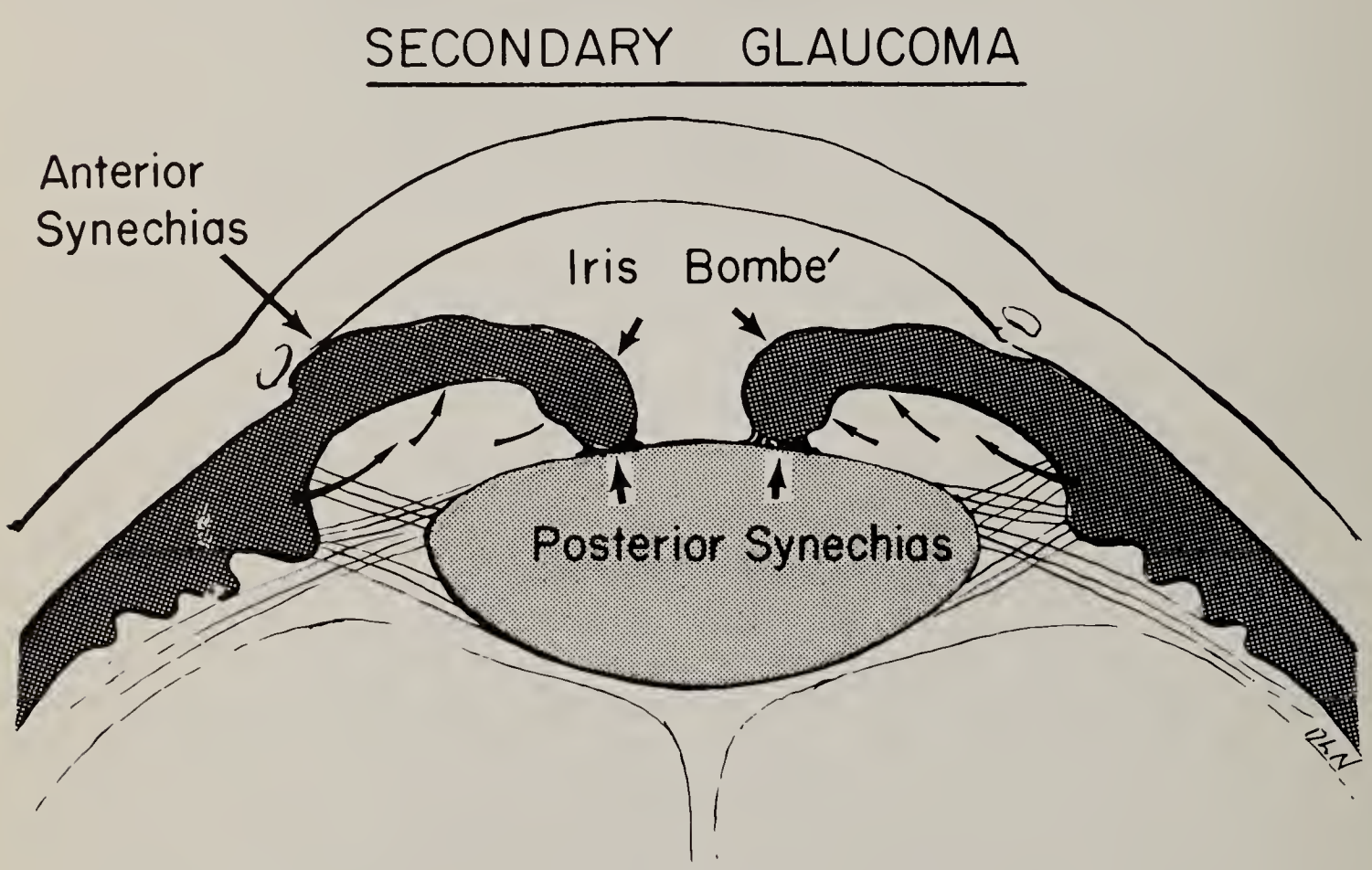
(FIG. 5)

Acute angle closure glaucoma represents an ocular emergency, because vision can be lost completely and permanently within a few days. Emergency treatment consists of the use of osmotic agents such as glycerol orally (about 1.0 Gm/Kg in lemon juice), or slow intravenous infusions of urea (1.0 Gm./Kg. in 30% solution, 60 drops or less per min.) or mannitol. Miotics such as pilocarpine are instilled frequently, and occasionally Diamox is used as a temporary measure. The osmotic agents usually succeed in reducing the intraocular pressure to normal. As soon as the acute congestive signs have subsided, certainly within 1 to 3 days, surgery is indicated to eliminate the physiologic iris bombe effect which closed the filtration angle. This is accomplished by a peripheral iridectomy which restores free communication between the posterior and anterior chambers (Fig. 5). If adhesions (peripheral anterior synechias or "P.A.S.") have not formed between the root of the iris and the trabeculum because of previous attacks or delayed treatment, such an iridectomy produces a permanent cure of angle closure glaucoma without the necessity of using any medical therapy.

Subacute or Chronic Angle Closure Glaucoma. Some individuals experience mild attacks of angle closure glaucoma characterized by blurring of vision, colored halos around lights, and mild aching under any situation which produces dilatation of the pupil. Such attacks may be relatively brief and subside spontaneously. However, repeated attacks result in permanent peripheral anterior synechias to the trabeculum with diminution of facility of outflow of aqueous. If such adhesions have developed over most of the drainage angle, medical treatment or a simple iridectomy is not effective, and a filtering operation such as used in open angle glaucoma becomes necessary. Since a filtering operation in such cases is fraught with complications as contrasted with a simple curative iridectomy in early cases, it is the responsibility of the physician and ophthalmologist to detect such cases early when an iridectomy can still be done successfully.

SECONDARY GLAUCOMA

There are many causes of glaucoma secondary to other ocular disease. Most of these result in blocking of the trabeculum and the canal of Schlemm by adhesions or debris; e.g., anterior chamber hemorrhage following blunt injury to the eye, formation of vascularized scar tissue in the angle secondary to occlusion of the central retinal vein or in advanced diabetics with retinopathy, blockage of the trabeculum with lens cortex in cases of hypermature cataracts or swollen lenses in intumescent cataracts, recession of the angle with late glaucoma following injury, etc. Probably the most common cause of secondary glaucoma follows iritis with formation of posterior synechias and pupillary block which prevents circulation of aqueous from the posterior to the anterior chamber (Fig. 6). The angle and trabeculum becomes occluded not only by the iris bombe effect but also by inflammatory debris. The iris bombe effect can be minimized by widely dilating and moving the pupil by mydriatics so that there is less constant contact of the posterior surface of the iris with the anterior surface of the lens. It is beyond the scope of this article to discuss the details of the mechanism and management of secondary glaucoma.



(FIG. 6)

SUMMARY

A brief description has been given of the etiology, diagnosis, and management of the most common forms of glaucoma in adults. Open angle glaucoma must be detected in its early stages by routine measurement of tension with the Schioetz tonometer by both general physicians and ophthalmologists in patients over 40 years of age. Because treatment prevents rather than restores vision, proper medical treatment usually prevents further loss of vision although occasionally an external filtering operation is necessary to reduce intraocular pressure to normal. Angle closure glaucoma, with either acute or subacute symptoms, is a surgical problem which can be cured in the early stages by simple iridectomy.

ETIOLOGY AND TREATMENT OF THE CORNEAL HOMOGRAFT REACTION INCLUDING AZATHIOPRINE (IMURAN)

William F. Hughes, M.D.[1]
Jeffrey Kallmeyer, M.B., M.Med. (Int.)[2]

Grafts of tissues of organs exchanged between genetically different individuals are ultimately destroyed by the recipient on the basis of an antigen-antibody reaction. During the past decade, a large amount of work has been done to elucidate this reaction, much of it connected with the cornea. It may be profitable to review some of this work as it applies to the homograft reaction which can follow corneal transplantation.

ANTIGEN

Although the exact biochemical source of the antigen responsible for the production of isoantibodies which destroy homografts or heterografts is unknown, there is considerable information on the basic characteristics of such an antigen.

Number of Living Cells. Viable cells are necessary to elicit the homograft reaction; the greater number of cells, the greater likelihood of a homograft reaction. In the cornea, most of the nuclear material resides in the epithelium. After corneal transplantation, the epithelium of the donor is probably replaced by the host within a period of days or weeks. To anticipate this and also reduce the amount of antigen, many corneal surgeons remove the epithelium from the donor button. The corneal stroma, underlying the epithelium, contains relatively few connective tissue-like cells, and the endothelium consists of a single layer of cells on the posterior surface of the cornea in contact with the aqueous. The relatively few cells may be a partial explanation why corneal homografts lead a charmed existence similar to cartilage, fascia, bone, fat and arteries; unlike the homografts of skin and most other tissues. Killing the cells by freezing two weeks after experimental corneal transplantation in rabbits further lessens the homograft reaction.[1] The reaction does not occur after lamellar transplantation of the anterior layers of the cornea from non-viable donor material preserved by dehydration, even in heterografts.[2]

Source of Antigen. The antigen responsible for graft rejection is genetically and not organ specific, as evidenced by: (1) the absence of necrotizing reaction in skin grafts transferred between monozygotic twins,[3] and (2) the potentiation of the "second set" type of homograft reaction when skin and corneal epithelium are used interchangeably, or when spleen, thymus, lymph nodes, or leucocytes from the donor are used to hasten and augment skin homograft reactions.[4-6] Although corneal homograft reactions usually develop within a few weeks after operation, they can appear after more than a year. This implies that some of the

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donor antigen is still present after a long period of time, and that the donor is not completely replaced by host cells during this period. This has been substantiated by rabbit experiments in which DNA in the stromal and endothelial nuclei has been labelled with the radioactive isotope, tritiated thymidine. Endothelial cells have been found to persist for one year and stromal cells for two years after transplantation.[7,8] Using immunoelectrophoresis and agar diffusion technics, precipitin antibodies to corneal stroma antigen can be easily demonstrated during the first ten days after heterograft transplantation, with a progressive decrease during the first year.[9] Time-wise, this corresponds with the disappearance of the mucopolysaccharide ground substance of the stroma (Dohlman & Smelser[9]). The cells of the corneal stroma must be poorly antigenic, because cytotoxic effects in tissue culture of rabbit stromal cells could not be demonstrated after introduction of duck antiserum against whole rabbit corneas.[10]

The earliest manifestation of a homograft reaction is an invasion of blood vessels, lymphocytes, monocytes, and plasma cells into the host cornea, through a gap in Descemet's membrane posteriorly, to reach the endothelium which is destroyed peripherally in this area.[11] The extent to which the endothelium alone can elicit a homograft reaction has not been demonstrated.

The abundant collagen of the corneal stroma is probably not antigenic.[12] The DNA proteins probably have no antigenic activity, but may act as an adjuvant or vehicle for the antigen. "The substances responsible for the specificity of the transplantation antigens are probably similar to the blood group mucoids; i.e., amino acid polysaccharide complexes." Enhancing antigens are probably present in the cytoplasmic particles.[6]

Because fresh donor corneas with viable endothelium are usually necessary to obtain clear penetrating grafts, recent reports of storage methods to reduce the antigenicity of this material are interesting. If the donor cornea is stored within the corneal stroma of an animal of the same species,[13] or the donor human cornea is stored in human serum (especially that of the recipient),[14] the incidence of homograft reactions is apparently diminished. Intracorneal injection of 0.2 cc of 2% DNA prepared from calf thymus into the host cornea before transplantation has been suggested.[15]

ANTIBODY

It seems well established that lymphocytes and plasma cells are important in the production and/or transport of antibodies which produce graft rejections, and these cells with their antibodies can be passively transferred.[16] If the homograft is separated from such cells in sensitized animals by a porous filter which permits diffusion of fluids only, the graft is tolerated.[17,18] This suggests that the cytotoxins to homografts are transported by cells, probably lymphocytes. The corneal surgeon is well aware of the poorer prognosis to be expected after operations on corneas with subacute keratitis, with probable increase in the likelihood of homograft reactions.[19] It is fortunate that the cornea is isolated from circulating cells by the cell-free aqueous and the absence of blood vessels.

Although ABO antigens have been demonstrated in the human cornea and ABO antibodies in the aqueous,[20] no Rh antigens have been found in the cornea. Clinical correlations of blood group incompatiblity between donor and recipient and the development of homograft reactions have been inconclusive or negative.[21] In one small series, circulating precipitins to the donor cornea were demonstrated in the serum of eight of 14 cases of homografting in humans between the 5th and 20th postoperative day.[22]

Reduction of Immunological Reactivity. The importance of agammaglobulinemia in promoting tolerance of skin grafts has been disputed.[23] Immunological tolerance can be accomplished by inoculating animals during embryonic life or at birth with the adult tissue.[16]

Immunologic suppression can be accomplished by the administration of many agents,[24] or drugs used alone or in combination. One of the newer of these agents, azathioprine (Imuran*), will be discussed in more detail later in connection with the treatment of a case of severe corneal homograft reaction.

ANTIGEN-ANTIBODY REACTION

The incidence of homograft reactions following a lamellar corneal transplantation of the epithelium and stroma (not including Descemet's membrane and endothelium) is lower than that following transplantation of all layers of the cornea.[25] This might be due to the absence of endothelium and Descemet's membrane in the lamellar graft, but may be due also to the lack of contact with the aqueous. The association of vascularization with the development of a homograft reaction has been pointed out many times,[26] probably bringing cells and antibodies into contact with the homograft antigen. Pre-existing corneal vascularization, however, is not necessary as a prerequisite for the beginning of a corneal graft rejection, although the reaction itself is characteristically associated with invasion of the surrounding host cornea and later perhaps the graft.[27] The cornea has no true endothelial-lined lymphatic channels, perhaps another factor in the relative immunity of the cornea to a homograft reaction compared to other tissues.

Inhibition of Antigen-Antibody Reaction. The use of corticosteroids, both systemically and locally, has been an important weapon against the corneal homograft reaction. Of special value is the subconjunctival injection of 20 mg. (0.5 cc) of depoMedrol, a repository form of methylprednisone which gives a significant level of local steroid for perhaps 2-3 weeks at least. Although the systemic administration of steroids at the time of operation does not delay healing of the graft, subconjunctival depoMedrol apparently does so, especially in cases of corneal dystrophy which heal more slowly. Accordingly, subconjunctival depoMedrol or intensive local use of steroids is usually delayed a week or two if possible until initial healing has occurred. If two animals are subjected to a period of parabiosis or receive exchange transfusions prior to cross-grafting, much of the inflammatory reaction to homografts is eliminated.[28]

*Imuran, Burroughs Wellcome and Company, Tuckahoe, New York.

SUMMARY OF CHARACTERISTICS OF THE CORNEA AS A HOMOGRAFT

From the previous information, the cornea is considered a semi-privileged tissue as far as homograft rejections are concerned. Many corneal grafts have little inflammatory reaction, some have a moderately stormy postoperative course, and rarely does any serious necrosis ensue although the graft may become cloudy. This relative immunity to homograft reactions compared to other tissues may be due to: (1) relatively few cells after the epithelium has been desquamated and replaced by the host epithelium, so that the antigen stimulus is small; and (2) lack of close contact with vascular or lymphatic channels, and normal absence of cells in the aqueous, especially lymphocytes and plasma cells which are probably important in the production and transport of homograft and heterograft antibodies. Therapeutic weapons consist of: (1) use of preserved grafts for lamellar corneal transplantations; (2) removal of the corneal epithelium of the donor button to reduce the amount of cellular antigen; (3) possibly pre-treatment of the donor cornea in the recipient's serum; (4) use of steroids systemically and locally; and (5) use of immuno-suppressive agents such as Imuran as described in the following patient.

IMMUNO-SUPPRESSIVE TREATMENT WITH AZATHIOPRINE (IMURAN)

Various immuno-suppressive drugs have been used alone and in combination in an attempt to prolong graft survival.[29-33] In 1963, Cobb and Basu reported that the intraperitoneal injection of 6-mercaptopurine delayed the onset of vascularization, clouding, and cellular infiltration of lamellar grafts of beef corneas transplanted into stromal pockets of rabbit corneas.[34]

Azathioprine, an immuno-suppressive and antineoplastic agent, (a 6-mercaptopurine derivative) was noted originally by Calne *et al*[35] in 1961 and Zukoski and Callaway[36] to prolong survival of canine renal homografts. Since that time azathioprine has become the basic immuno-suppressive drug used in organ transplant. Most workers in the field of renal transplantation[37] use azathioprine in combination with one or more immuno-suppressive drugs. A combination of azathioprine and steroids has been accepted by many authorities. Merrill[38] has employed doses of azathioprine varying from 2 to 7 mg/kg daily in combination with prednisone 1 mg/kg in the treatment of patients with kidney transplants, although the optimal dosage appears to range from 2 to 4 mg/kg day. With the effectiveness of azathioprine and steroids in suppressing antibody response in mind, it was thought that a therapeutic trial of these two drugs was indicated in a patient who rejected a corneal graft in spite of the use of steroids locally and systemically.

Case Report. Mr. R. M., a 29 year old bartender, was admitted to the hospital in Feb. 1964, at which time a 6 mm. penetrating corneal transplantation was performed for a hereditary macular dystrophy of the right cornea. A subconjunctival injection of 20 mg. of depoMedrol was given after one week because of mild edema of the graft and inflammatory signs. Because vascularization proceeded through the host cornea to the edge of the graft after five weeks, another subconjunctival injection of depoMedrol was given, and he was started on dexamethasone 0.75 mg. tid systemically. At six weeks, evidence of poor healing developed and severity of the homograft reaction increased. Subconjunctival injections of depoMedrol were repeated at six and seven weeks postoperatively, and dexamethasone was increased to 3.75 mg. a day. A ring-shaped sloughing of the superficial peripheral portion of the graft developed, not unlike a Mooren's ulcer, so that only a 2 mm. central area remained intact (Color Plate #1). Because of this progressive necrotizing homograft reaction, azathioprine was started eight weeks postoperatively in a dose of 2.5 mg/kg, combined with 15 mg. of prednisone a day, for a period of 16 days. Baseline studies included hemoglobin, white blood and platelet count, serum electrophoresis, thymol turbidity, direct and indirect bilirubin and cephalin flocculation. The patient was kept hospitalized in protective isolation. At 10 weeks, another subconjunctival injection of depoMedrol was given. At this time the ulceration was healing and the infiltration and inflammatory signs of the homograft reaction were rapidly subsiding. At three months, there was no activity, but the graft remained scarred with vision of counting fingers at four feet (Color Plate #2). During the azathioprine therapy, the white count dropped to 2,850 and platelets to 62,500, but both rose rapidly to normal on withdrawal of the drug.

In November, 1964, a second penetrating corneal transplant, 7 mm. in diameter, was performed on the same eye without complications. After a few days, he began to show signs of an early homograft reaction, so he was given a subconjunctival injection of 20 mg. of depoMedrol. However, edema of the graft, vascularity around the graft, and the positive aqueous ray increased, so azathioprine and prednisone were started on the fifth postoperative day (Color Plate #3). The dose of azathioprine was 4 mg/kg/day in divided doses for the first two days of therapy, thereafter a

maintenance dose of 2.5 mg/kg. prednisone was also given in doses of 30 mg/day for two days and thereafter 20 mg/day. Three weeks postoperatively, most of the homograft reaction had subsided with only mild congestion, haziness of the graft and slightly positive aqueous ray (Color Plate #4).

With the exception of the hemoglobin, white blood and platelet counts, blood studies remained normal over a period of two months. The serial hematologic changes are summarized in graphic form (Fig. 1). Severe bone marrow depression necessitated re-hospitalization five weeks after beginning therapy. At this time he was mildly febrile (101° orally), which was attributed to acute pharyngitis. A bone marrow aspiration on admission showed severe generalized hypoplasia with increased stainable iron. Serum iron was 169 mcg; total iron binding capacity was 252 mcg. A regimen of strict isolation was instituted, prednisone was increased to 100 mg. daily and testosterone propionate 100 mg. daily was added. The course was uneventful, and he was discharged 24 days later following gradual but marked improvement in bone marrow and peripheral blood picture.

The corneal graft continued to clear, and three months postoperatively, vision could be corrected to 20/30 with a correction of $-4.00 + 5.50 \times 15°$ (Color Plate #5.)

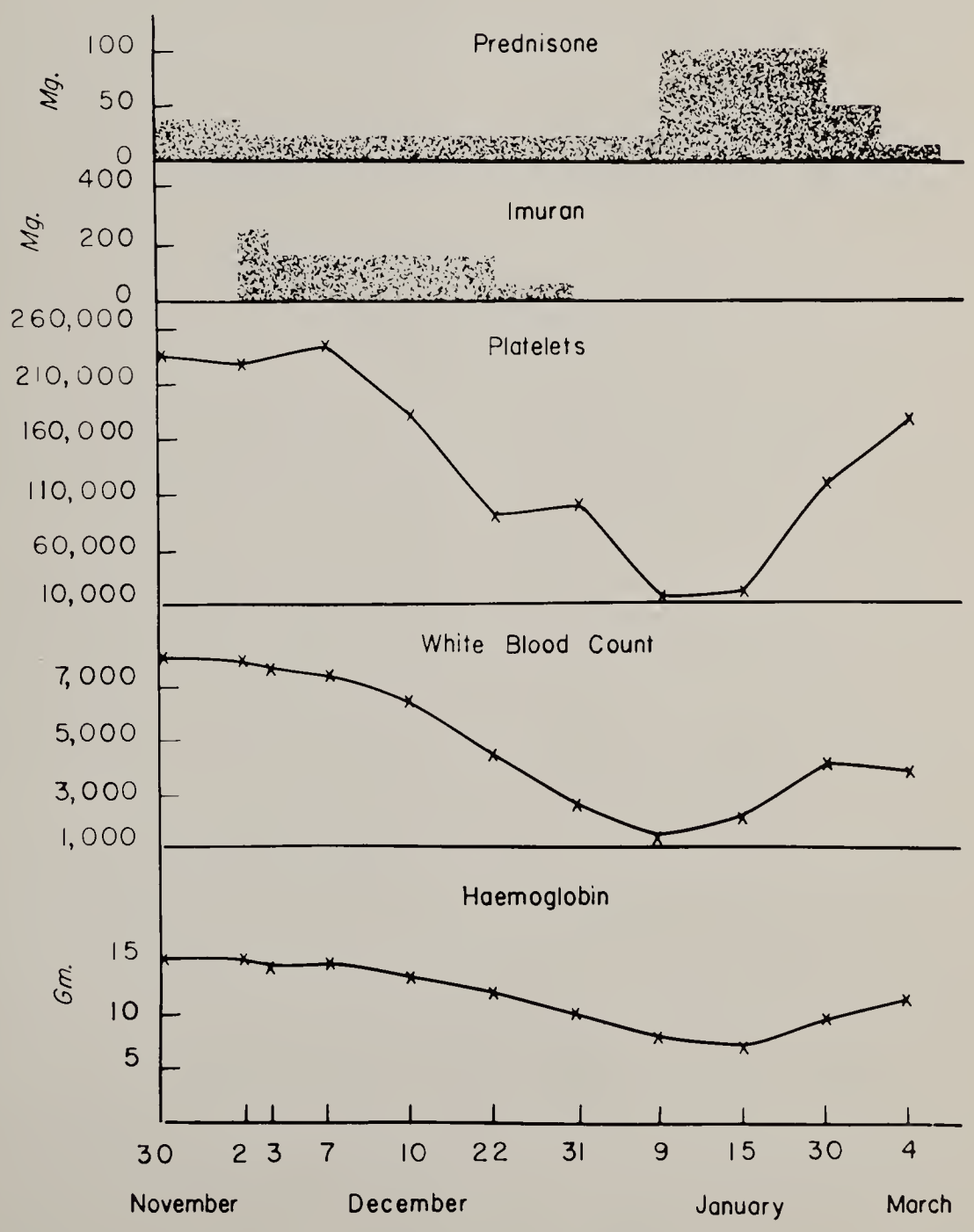

Fig. 1—Hematologic Changes Associated with Imuran Treatment.

DISCUSSION

The growth-inhibitory effects of azathioprine on hematopoietic tissues seem to be identical with that of other active thiopurines such as 6-mercaptopurine and thioguanine. Others have reported suppression of granulocytes and occasional mild anaemia. No significant changes in platelet count have been reported. Rudles *et al*[39] administered azathioprine in doses of 1 to 2 mg/kg daily for an almost indefinite period without signs of toxicity. This case showed severe bone marrow depression on a maintenance dose as low as 2.5 mg/kg daily. The highest percentage of deaths in the post-renal transplant periods[40-42] are attributed to antimetabolite toxicity. Kolff *et al*[43] reported, with use of smaller maintenance doses of azathioprine, a marked reduction in the morbidity and mortality of renal transplantation. They feel a more conservative approach to the use of immunosuppressive drugs is indicated at the present.

SUMMARY

The literature has been reviewed briefly to point out some of the reasons why corneal homografts can be transplanted successfully. The factors which induce a corneal homograft reaction, and the methods available to prevent and treat such an antigen-antibody reaction have been discussed. A case is presented in which two homograft reactions failed to respond to the local and systemic administration of corticosteroids, but did respond to the administration of azathioprine (Imuran) with an eventual clear graft. This treatment was complicated by severe bone marrow depression which recovered.

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TREATMENT OF DIABETIC RETINOPATHY

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One of the most discouraging problems facing both the internist and ophthalmologist is the management of severe diabetes with rapidly progressing retinopathy, usually occurring in the younger age group.[1] In Britain, where a National Registry is maintained, diabetes is listed as the number one cause of all blindness, and it is the third leading cause of blindness in the United States.

The etiology of vascular changes in diabetes is unknown, and may even be secondary to other retinal changes in the central deep portion of the retina. For this reason many empirical treatments have been tried, the foremost being strict control of diabetes, the other agents probably not being more effective than the insulin preparations. Many authors believe that early diagnosis and careful control of the disease over the years tends to keep whatever retinopathy occurs at a minimum level. Of doubtful value is the administration of Vitamin B^{12}. The results of seventeen surgical adrenalectomies reported in the 1962 symposium are not encouraging.[2,3]

Of possible value are the following: (1) photocoagulation of peripheral areas of retinitis proliferans; (2) transcleral diathermy; (3) low fat diet; and (4) various preparations of Testosterone and related steroids.

1. Photocoagulation[4,5]. In 1958 Meyer-Schwickerath disclosed his treatment of retinitis proliferans with his photocoagulator after having observed chorioretinal lesions induced by solar energy (eclipse burns) and atomic energy (atomic detonation flash). Meyer-Schwickerath's modified instrument is still the preferred light source for photocoagulation of advanced diabetic retinopathy, although ruby lasers are being employed experimentally in several laboratories. The aim of this treatment is to coagulate all newly formed vessels in order to prevent profuse retinal and vitreous hemorrhages leading to retinitis proliferans and retinal detachment. Meyer-Schwickerath and other early investigators attempted to photocoagulate almost all hemorrhagic lesions, including small microaneurysms. This was found to be excessively destructive. As a general rule now, photocoagulation is applied to pre-retinal vessels in areas of hemorrhages which are grouped together at points away from the disc and macula. Unfortunately, retinitis proliferans has a predilection for the optic disc which cannot be photocoagulated without complications.

2. Diathermy. Another local treatment of diabetic retinopathy is trans-scleral diathermy of the retina[6], on the basis of observations that diabetic retinopathy is less severe when the retina has post-inflammatory chorioretinal scars prior to the development of diabetes. Trans-scleral diathermy is applied to the superior and inferior temporal quadrants of the retina, similar to the technique used for retinal detachment. While no outstanding complications of this procedure have been reported, the results are not particularly convincing.

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3. **Low Fat Diet:** The concept of management of fat metabolism of the patients with diabetic retinopathy started accidentally when hypertensive patients were put on a rice diet. Because diabetics tend to have elevated serum lipids, Van Eck[7] and King and Dobree[8] treated diabetic patients with a low saturated fat diet of 20 Gm. a day, and noted reduction in retinal exudates without visual improvement. Esman and others reported the disappearance of waxy exudates in diabetic retinopathy during administration of para-amino salicylates (PAS)[9]. The carbohydrate content of the patient's diet was reduced, but the amount or kind of fat was not restricted. The cholesterol content in the blood of these patients decreased. In all of this work designed to lower the blood fats, it should be remembered that the hard waxy exudates may be the end result of retinal degeneration rather than a primary deposition of lipids.

4. **Various Preparations of Testosterone and Related Steroids:** There have been both encouraging and negative reports on the value of testosterone and related hormones in the treatment of diabetic retinopathy[10–13]. They have a pronounced anabolic action, activating protein synthesis, with only a slight virilizing effect. They reduce the insulin requirement. Houtsmueller especially felt that early normalization of the blood plasma and reduction in blood viscosity (sludging) would improve retinal circulation and reduce the degree of diabetic retinopathy. Overall statistics on the value of this treatment are not significant.

HYPOPHYSECTOMY OR PITUITARY STALK SECTION

The most encouraging results in the treatment of diabetic retinopathy have been after induced hypopituitarism. In 1931, Houssay and Biasotti found that hypophysectomy partially alleviated experimental diabetes in animals, and that pituitary factors aggravated the diabetic state[14]. Luft *et al* reported in 1952 encouraging results following ablative hypophysectomy in 10 patients with juvenile diabetes[15,16]. In 1953, Poulsen reported remarkable improvement in the diabetic retinopathy of a woman who developed hypopituitarism postpartum[17]. In the symposium of 1962, the effect on diabetic retinopathy of induced hypopituitarism was discussed; including 103 surgical hypophysectomies, 20 hypophyseal stalk sections (which interrupts the arterial blood supply to the anterior lobe), and 11 yttrium[90] implantations.[2] The overall operative mortality was about 11% and about ⅔ of the patients showed either an improvement of vision or an apparent slowing of the progression of the retinopathy. Similar results were reported in 61 cases by Lawrence in which hypopituitarism was produced by the localized irradiation by 11,000-15,000 rad from the proton beam of a cyclotron accelerator.[18] McMeel and his group at Boston now report that 67% of their 80 pituitary stalk section cases have vision equal or better than prior to surgery.[19]

On the basis of these reported results, hypophyseal stalk sections were done on selected patients at the Presbyterian-St. Luke's Hospital by Drs. Eric Oldberg and A. B. Johnson largely under the medical management of Dr. Theodore Schwartz, beginning in early 1962. The basis for selection of patients followed the guide-lines set up in the 1962 symposium, including: (1) progressive hemorrhagic retinopathy and vascular proliferans; (2) loss of vision in one eye and threatened loss in the other eye; (3) fair kidney, cardiac, and neural function; (4) younger age group, e.g. under 50; and (5) good motivation and understanding by the patient. During the past 2½ years, 8 patients have met these criteria at our hospital. The average age of these patients was 33, and they had had diabetes for an average of 20 years. The average followup of the retinopathy, including documentation by fundus photography, is 2 years postoperatively.

The results of the 8 patients treated by hypophyseal stalk section via the transfrontal route at the Presbyterian-St. Luke's Hospital are tabulated in Table 1. There were no operative mortalities, in line with the fact that hypophyseal stalk

section is less dangerous than hypophysectomy. One patient (E.M.) had an immediate postoperative visual field change suggesting a lesion of the left inferior portion of the optic chiasm and left optic nerve, but this gradually improved after several weeks. Evidence of hypopituitarism appeared in all patients, with marked decrease in insulin requirement and development of the need of replacement therapy in the form of thyroid and hydrocortisone. One patient (D.W.) died of myocardial infarction about 9 months after surgery. His retinopathy had continued to progress. The health of the remaining 7 patients has not deteriorated since the operation. The ocular results showed definite improvement in 4 cases, with maintenance or improvement of vision, reduction in retinal and vitreous hemorrhages, fewer exudates, and improvement of the vascular retinitis proliferans and dilatation of retinal veins. In one patient (R.D.) with early proliferation of capillary tufts into the vitreous from the lower portion of the disc (Color Plate #6), such vessels became completely bloodless without scar tissue proliferation following stalk section (Color Plate #7). One patient (J. L.) showed evidence of disappearance of microaneurysms and hard exudates (Color Plates #8, 9). Two patients (J. L. and S. K.) showed clearing of preoperative vitreous hemorrhages in one eye, leading to dramatic improvement of vision in that eye. Another patient (M. M.) showed complete disappearance of a rather large retinal and preretinal hemorrhage after surgery. Two patients (E. M.

TABLE 1

Diabetic Retinopathy Treated by Pituitary Stalk Section

PATIENT	EYE	VISION		IMPROVEMENT IN RETINOPATHY (+)				COMMENT
		Preop.	Postop.	Ret. H.	E.	Vit. Hem.	Vascular Prolif-erans	
J.L.	R.	20/20	20/20	+2	+2			Improved
	L.	C.F.	20/25	?+	?	+4	?+	Improved
M.M.	R.	20/20	(cataract) 20/25	+2	+2	+1	+1	Improved
	L.	L.P.	L.P.	?	?	?	?	Hem. Glc. Preop.
S.K.	R.	C.F.	20/40	+4	?	+3	+2	Improved
	L.	C.F.	20/300	+4	?	+3	+2	Improved
R.D.	R.	20/50+	20/30	+2	+2		+4	Improved
	L.	L.P.	L.P.	?	?	?	?	Ret. Detach & Glc. & Cat. Preop.
E.M.	R.	20/300	C.F.	0	0		—2(R.D.)	Immediate p.o.
	L.	20/40	20/60	+2	+2	+1	0	field loss
J.S.	R.	20/400	H.M.	?	?	0	—2	Ret. Detach.
	L.	20/70	20/60	+	+	—4	0	3 PO Vit. Hem.
G.F.	R.	20/30	20/200	0	0	—4	—2	Poor result
	L.	20/100	L.P.	0	0	—4	—4	Poor result
D.W.	R.	L.P.	No L.P.	0	0	0	0	Died PO 9 mos.
	L.	2/30	20/70	?	?	?	?	myocard. infarct. Bil. Glc.

*C.F. = Counting Fingers Only
L.P. = Light perception only
Hem. Glc. = hemorrhagic glaucoma
E = retinal exudates
Ret. Detach. = retinal detachment
Cat. = cataract
Ret. H. = retinal hemorrhages
Vit. Hem. = vitreous hemorrhage

and J. S.) had a postoperative course which is difficult to evaluate, but might be considered to be some reduction in the rate of progression of the expected retinopathy. One patient (G. F.) continued to show progression of the retinopathy over 2 years after operation.

In summary, over this relatively short-term followup averaging 2 years after pituitary stalk section, 4 patients showed definite improvement in the retinopathy, 2 patients perhaps held their own, 1 patient became progressively worse, and 1 patient died 9 months postoperatively of a myocardial infarction with progressive worsening of the retinopathy. The results in this small series therefore approximate those reported previously after induced hypopituitarism.

COMMENT

The accumulating evidence indicates that the empirical treatment of diabetic retinopathy by induction of hypopituitarism improves or at least slows the rate of rapidly progressing blindness in about ⅔ of the cases. Because spontaneous exacerbations and remissions are characteristic of diabetic retinopathy, evaluation of any treatment is notoriously difficult. At the very least, detailed drawings and photographs in the same areas are necessary over a long period of time, both in the treated and control cases. Unfortunately, there is little objective data on the rate of progression of retinopathy in various types of diabetics and only the opinion of the physician is available. Certainly, careful repeated examination and pictorial recordings of the fundi over a period of time affords the physician the best indication of rate of progressiveness of the retinopathy. In general, the development of microaneurysms and hard exudates in an older diabetic does not have dire forebodings of blindness within a relatively short period of time. However, the physician is properly concerned about the appearance of vascular retinitis proliferans in a relatively young individual. Even a few capillary tufts growing out into the vitreous probably indicates serious underlying retinal involvement. Perhaps the overall vascularity of the fundus is important, including dilatation of the larger veins. Larger retinal, pre-retinal, and vitreous hemorrhages are certainly an indication of severe vascular damage. However, in the evaluation of the results of any treatment it must be remembered that even large hemorrhages can absorb spontaneously and can result in a spectacular improvement of vision.

There are several reasons for conservatism in the selection of candidates for hypophyseal stalk section or perhaps any method of induced hypopituitarism: e.g., (1) the lack of success in at least a third of the cases; (2) the slight danger in the procedure itself; and (3) the often distressing alteration of hormonal balance postoperatively which requires rather close supervision by the physician. However, the encouraging results in many of these cases of rapidly progressive retinopathy with blindness already present in one eye would indicate the desirability of such a procedure if all of the criteria for the selection of patients outlined previously are satisfied.

SUMMARY

Various dietary, drug and surgical approaches to the therapy of severe diabetic vasculopathy are described. An evaluation of the empirical treatment of diabetic retinopathy indicates that induced hypopituitarism may be the treatment of choice in carefully selected patients with rapidly progressive vascularizing retinopathy. The results of 8 patients treated by hypophyseal stalk section at this hospital have been presented.

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HERPES SIMPLEX KERATITIS

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Herpes simplex keratitis is the most important and frequently diagnosed specific inflammation of the cornea in this country. With the advent of local and systemic steroid therapy for ocular disorders, herpetic keratitis is becoming more frequent and severe, and previously rare bilateral cases are seen more commonly. This review will summarize some of our knowledge of the virus, and some aspects of the medical and surgical treatment of herpetic keratitis.

Characteristics of the Virus. Herpes simplex is the best known member of the classic herpes virus group. It is a DNA virus and is very sensitive to heat or drying. Infectivity is not well retained at −20° C., and storage at −60° C. is recommended. Ether and the quaternary ammonium detergents (Zephiran) destroy infectivity, but glycerol does not.

Herpes simplex virus has a special affinity for cells of ectodermal origin, and grows readily in skin, mucous membrane and corneal epithelium. On tissue culture, it grows in a wide variety of cells, including epithelial cells from rabbit kidney and HE LA cells. When the virus is introduced into a tissue culture, the earliest evidence of infection is an inhibition of mitosis. Within 6 hours, there is a definite increase in the desoxyribonucleic acid (DNA) of the host cell. During the eclipse phase of 12 hours, the virus cannot be demonstrated by infectivity or reactivity with specific antigen. Mature viral particles begin to be released into the medium some 15 hours after the original inoculation. Intranuclear inclusions are at first basophilic and contain virus, and later become eosinophilic and do not contain virus. Cell necrosis is the end result of infection with herpes virus.

Biology and General Course of the Disease in Humans. The two major forms of herpes simplex keratitis are illustrated in Figure 1. The classic and most common form of the disease is a dendritic ulcer, an infection of the superficial corneal epithelium with ulceration and staining with fluorescein in a characteristic branched-tree pattern. The configuration of this lesion is specific for herpes simplex infection. It is generally unilateral, and virus can be isolated from the ulcer in 50-70% of cases. Recurrence in the same eye occurs frequently, and the disease may eventually progress to stromal involvement in 5-15% of cases. Dendritic ulcer may also heal without involvement of the underlying corneal stroma, and therefore leave no scar or resulting visual disability.

The deep stromal form of herpetic keratitis results in varying degrees of scarring and decrease in vision. Because the virus has not been isolated from stromal disease, an immune reaction has been postulated. If so, then local tissue hypersensitivity probably plays a major role, because both superficial and stromal forms occur in the presence of a high and constant amount of serum neutralizing antibodies to herpes simplex virus.

Treatment of Dendritic Ulcer. Virus is not present in the conjunctiva, but only in the corneal epithelium. Therefore, removal of the infected epithelium with a margin of normal corneal epithelium is designed to remove the virus

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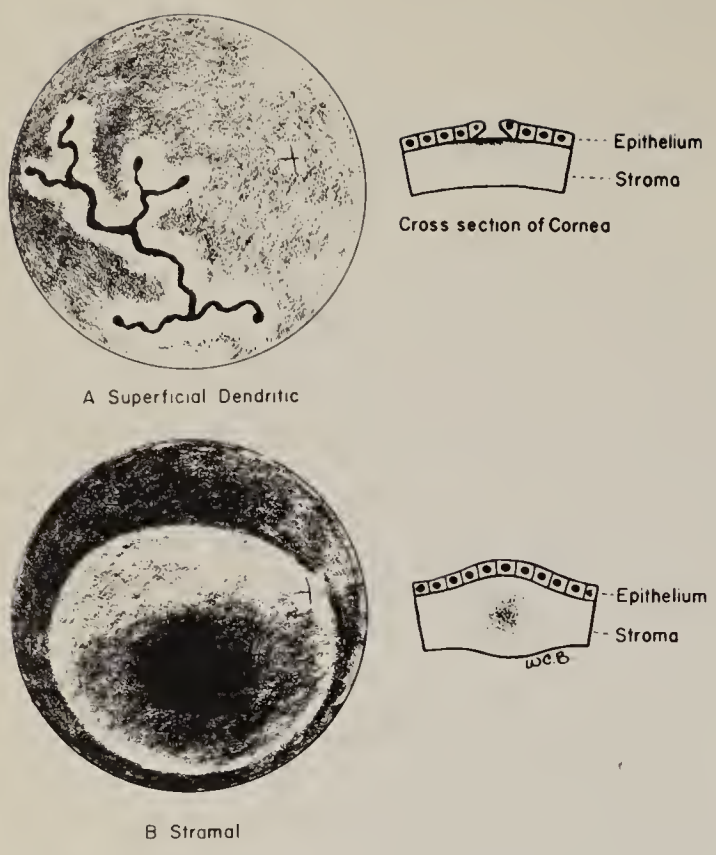

Fig. 1—The two major forms of herpes simplex keratitis.

and cure the dendritic ulcer. To facilitate removal of the infected corneal epithelium with a scalpel, many types of cauterizing agents have been utilized; most commonly 2% iodine or ether. Reported results with these methods show a cure rate of 65-90%; compared to spontaneous cures of 10-50%.

In 1960, Tamm reported that antimetabolite inhibitors of DNA synthesis suppressed the multiplication of viruses in tissue culture.[1] Idoxuridine (IDU), a DNA antagonist, was first suggested as a local treatment for dendritic ulcer by Kaufman in 1962.[2] Used as 0.1% drops every hour during the day and every two hours at night, he reported a beneficial effect in non-immune rabbits. Most of this work was repeated in the Microbiology Laboratory of the Presbyterian-St. Luke's Hospital in a combined project with Drs. A. W. Holmes and Friedrich Deinhardt. We found such treatment in non-immune rabbits less effective. There was an initial drop in recoverable virus and an improvement in clinical disease on treatment with idoxuridine for 2 to 3 days. However, during the last 3 days on treatment, the virus titer rose and clinical disease became worse so that at the end of observation little difference could be seen between treated and untreated animals. As the adult form of the human disease occurs in the presence of serum antibodies, we performed a similar experiment in immune rabbits (Figure 2). The rabbits were inoculated with herpes simplex virus on the cornea. No clinical disease resulted but they developed neutralizing antibody titers. Re-inoculation of these animals and treatment with idoxuridine showed little beneficial effect in either the virological or clinical course between the treated and untreated animals. Comparison of the non-immune and immune rabbits indicated that herpetic keratitis in rabbits was more dependent on the immune status than on idoxuridine therapy.

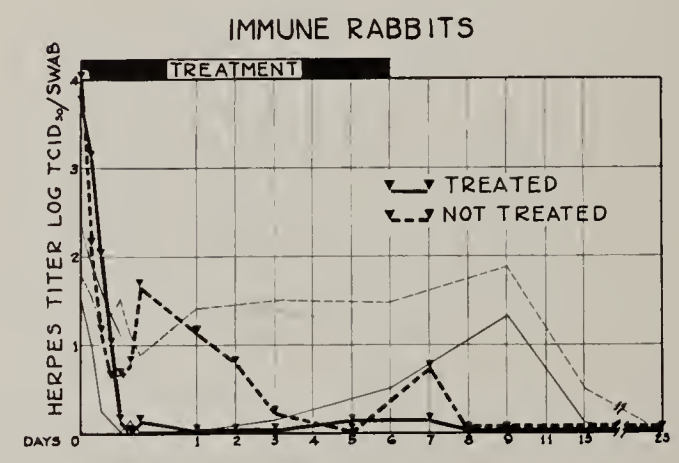

Fig. 2—Effect of idoxuridine treatment on serial virus titers in eyes of immune rabbits. Data of nonimmune rabbits are represented by light lines.

Our failure to demonstarate a dramatic clinical effect in rabbits led to tissue culture experiments. It was found that virus and idoxuridine could be incubated together in the absence of cells for 18 hours without affecting the virus' infectivity. Thus, there is not direct action of idoxuridine on the herpes simplex virus itself. Rather, the inhibition by idoxuridine of virus multiplication in tissue culture must be an indirect effect on the DNA metabolism of the cells on which the virus is dependent. The possibility exists that cellular synthesis of viral nucleic acid and protein may follow other pathways than those used by the cell in manufacturing its own component.

If this were the case, one would expect it possible to suppress production of infectious virus without interfering with cell multiplication. In experiments comparing virus titer and the number of tissue culture cells at varying concentrations of idoxuridine, it was found that the antimetabolite was equally toxic to both virus and cells (Figure 3). Therefore, from these results, it is incorrect to speak of a specific antiviral effect of idoxuridine.

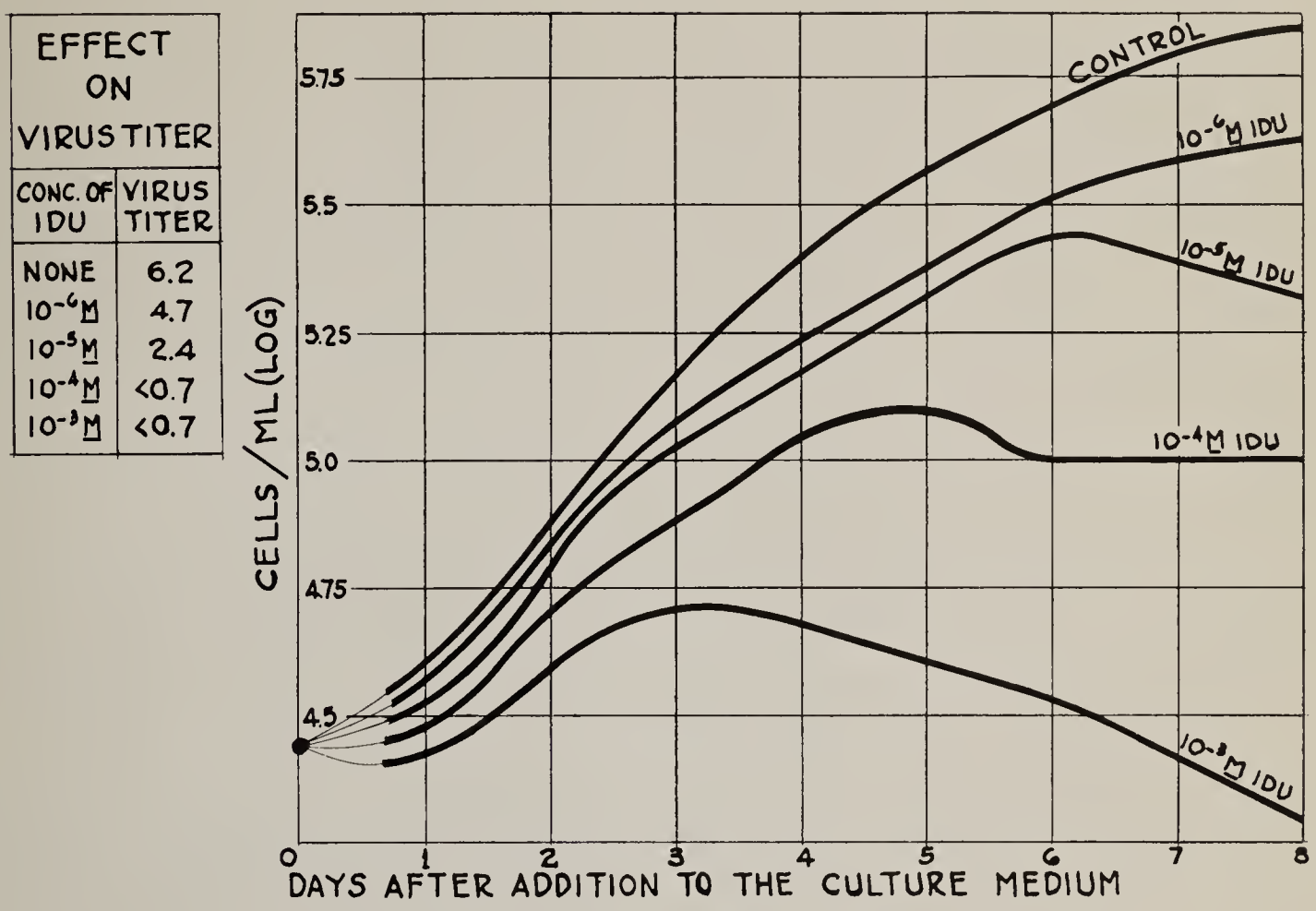

Fig. 3—Effect of idoxuridine on cell multiplication and production of infectious virus in tissue culture.

TABLE 1

Results in Treatment of Dendritic Ulcer with Idoxuridine
(uncontrolled cases)

Author*	No. Patients	Healed	Recurrences
Kaufman (1962)	76	99%	11%
Corrigan (1962)	15	100%	—
Maxwell (1963)	1216	80%	—
Havener (1963)	26	81%	—
Gilkes (1964)	82	99%	—
Ey et al (1964)	36	72%	11%
Maxwell (1965)	865	80%	—
Totals	2316	81%	11% (112 cases)

*References 3-9

TABLE 2

Results of Idoxuridine Treatment vs. Placebo

Author*	No. Patients	Healed	Recurrences
Burns (1963) IDU	23	65%	—
Placebo	15	33%	—
Patterson (1964) IDU	43	74%	16%
Placebo	41	15%	2%
Jepson (1964) IDU	12	92%	—
Placebo	12	58%	—
Laibson (1964) IDU	35	60%	34%
Placebo	53	21%	17%
Luntz (1963) IDU	11	55%	10%
Placebo	11	64%	18%
Total IDU	124	69%	22%
Placebo	132	27%	11%

*References 10-14

TABLE 3

Chemical Cautery and Curettage vs. Idoxuridine

Author*	No. Patients	Healed	Recurrences
MacKenzie (1964)			
IDU gtts.	25	44%	24%
IDU ung.	28	64%	—
Carbolization	27	96%	11%
Davidson (1964)			
IDU gtts.	25	56%	16%
Iodine	25	80%	4%
Total IDU	78	55%	20%
Chemical	52	88%	10%

*References 15-16

The results of treatment of dendritic ulcer in humans with idoxuridine have been reported by many authors, 81% of the patients being cured in an average of 7 days (Table 1). Recurrence rate and progression to stromal disease were not reported often because of the short term follow-up. These initial enthusiastic results have been tempered by other series with controls in which 15-64% of patients treated with a placebo healed spontaneously (Table 2). This emphasizes the extreme variability in the natural history of superficial herpetic keratitis. However, idoxuridine cured 69% of the cases compared to 27% of those given a placebo. This demonstrates that idoxuridine is more effective than placebo treatment in early dendritic ulcer, although the recurrence rate was 22% for the idoxuridine treated group vs. 11% for the placebo group. But the question remains whether idoxuridine treatment is more effective than standard treatment with chemical cautery and curettage. In the two reported series, chemical cautery and curettage cured 88% of dendritic ulcers while idoxuridine cured 55% (Table 3). The incidence of recurrence was 20% in the idoxuridine treated group vs. 10% for the chemical cautery and curettage group.

A summary of these tables indicates that (1) idoxuridine is more effective than placebo treatment; (2) spontaneous healing can be expected in approximately

30% of cases; (3) recurrence rates are higher with idoxuridine therapy (20 vs. 10%) than placebo treatment or chemical cautery and curettage; and (4) chemical cautery and curettage is a more effective way of treating superficial herpetic keratitis than idoxuridine.

But with all this data, the incidence of stromal disease and resulting visual disability is lacking. The form of treatment that reduces this complication will be the preferred method. Idoxuridine may be deficient here also. Most authors report a peculiar ground glass appearance of the superficial corneal stroma following treatment and healing of a dendritic ulcer with idoxuridine (Figure 4). These opacities gradually resolve, but have been noted as long as a year after treatment. Their exact nature is unknown. We have postulated that they may be related to the relatively slow elimination of virus and diseased cells, permitting virus or abnormal cellular antigens to be present sufficiently long to produce an antigen-antibody reaction and opacity of the underlying stroma.

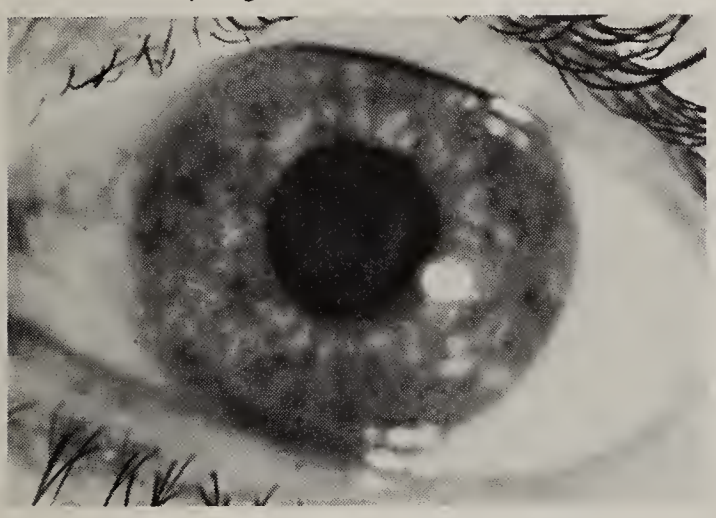

Fig. 4—Healed dendritic ulcer six weeks after idoxuridine therapy, showing residual stromal opacities.

Treatment of Stromal Herpes Simplex Keratitis. The deep form of herpetic keratitis has no recoverable virus, and may be an antigen-antibody reaction. If so, the local use of steroids might be expected to be beneficial. However, steroids can activate a latent virus and a recurrence of a dendritic ulcer can ensue. Although idoxuridine alone is admittedly ineffective in stromal disease, some ophthalmologists have recommended its use with steroids to protect against reactivation of the virus during steroid therapy of stromal herpes. Adequate clinical data is not available to evaluate this therapy, but certain facts are becoming evident. Pollack and Rose have shown that idoxuridine inhibits stromal wound healing in rabbits.[17] Local steroids also do this. Accordingly, it is not surprising that this combination has been incriminated in recent reports of perforation of the cornea.

The surgical treatment of stromal herpes keratitis involves removing the infected or scarred tissue and replacing it with new homograft cornea. In general, grafting is indicated in those chronic cases with deep ulceration and beginning vascularization, as a therapeutic measure to promote healing. This may consist of a partial thickness or lamellar graft using either fresh or dehydrated material, or a full thickness penetrating graft if the cornea has perforated. If the inflammation has subsided leaving a corneal scar and poor vision, a penetrating corneal transplantation can be performed to improve vision. Recurrences of herpetic keratitis only rarely occur in the corneal grafts.

SUMMARY

The manifestations of corneal infection by the herpes simplex virus and their treatment have been discussed. Idoxuridine has been shown to be more effective than a placebo in the treatment of superficial herpetic keratitis. It is not a specific anti-viral agent, but affects both cells and virus. The removal of infected epithelial cells by chemical cautery and curettage seems to be the most effective means of curing dendritic keratitis, with perhaps less tendency for recurrence.

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Fig. 1.—Severe corneal homograft reaction with clouding and peripheral sloughing of graft at beginning of treatment with Imuran.

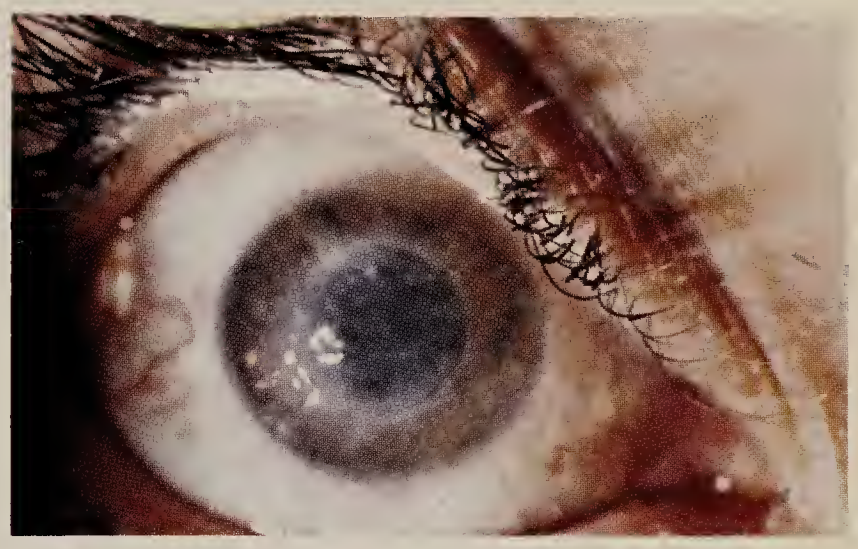

Fig. 2.—Two months after starting treatment with Imuran, showing subsidence of the inflammatory reaction and cessation of sloughing but with residual scarring of graft.

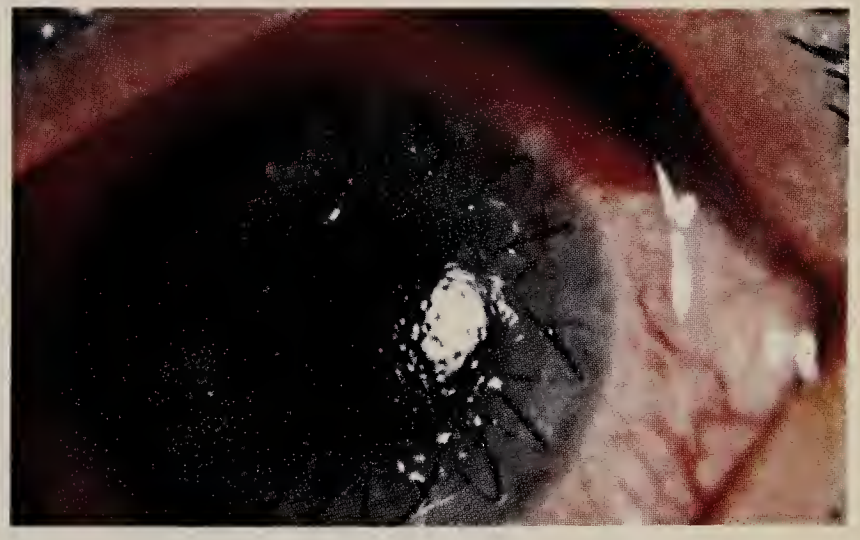

Fig. 3.—Twelve days following a second corneal graft, with early homograft reaction in spite of local and systemic steroids.

Fig. 4.—Fifteen days after starting Imuran, showing some clearing of graft and reduction in inflammation.

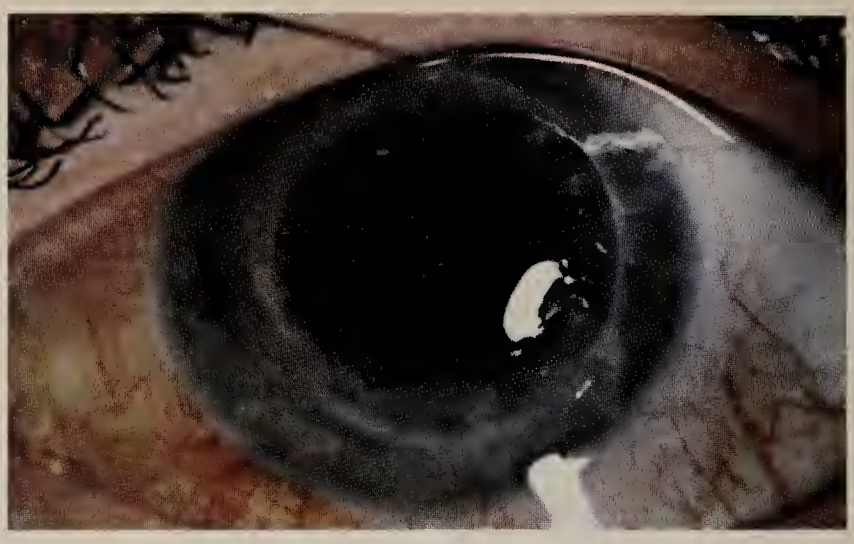

Fig. 5.—36 days after starting Imuran showing a clear corneal graft and subsidence of the homograft reaction.

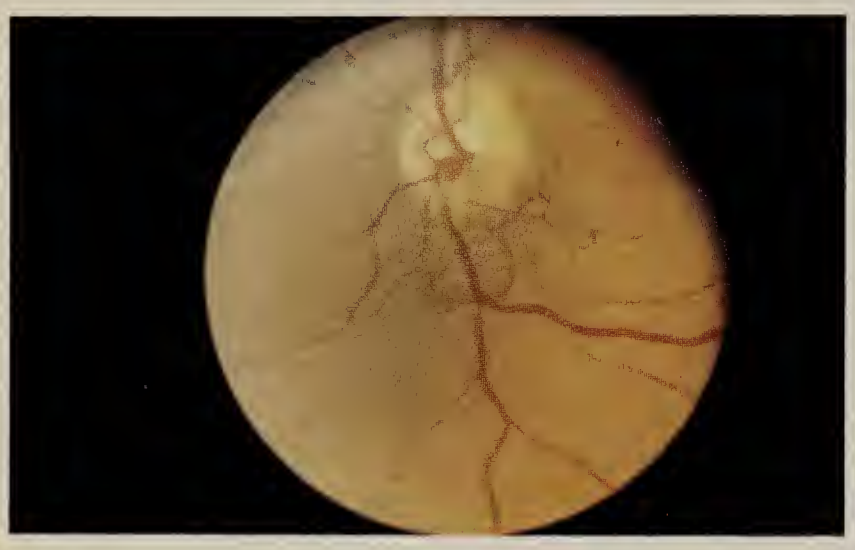

Fig. 6.—Diabetic patient (R.D.) with vascular retinitis proliferans coming from lower portion of disc, preoperatively.

Fig. 7.—Same eye as #6, 3 years after hypophyseal stalk section, showing conversion of vascular retinitis proliferans into bloodless white strands.

Fig. 8.—Diabetic patient (J.L.) with diabetic exudates and microaneurysms, preoperatively.

Fig. 9.—Same eye as #8, 2 years following hypophyseal stalk section, showing disappearance of exudates and microaneurysms in this area.

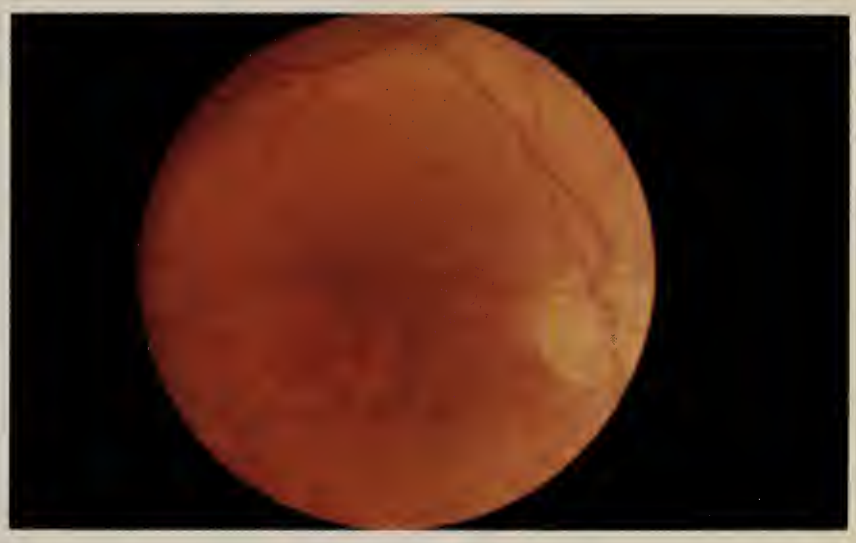

Fig. 10.—Patient (J.L.) with rheumatoid arthritis treated with chloroquine, showing annular pigmentation and degeneration of macula.

Fig. 11.—Post-photocoagulation final result.

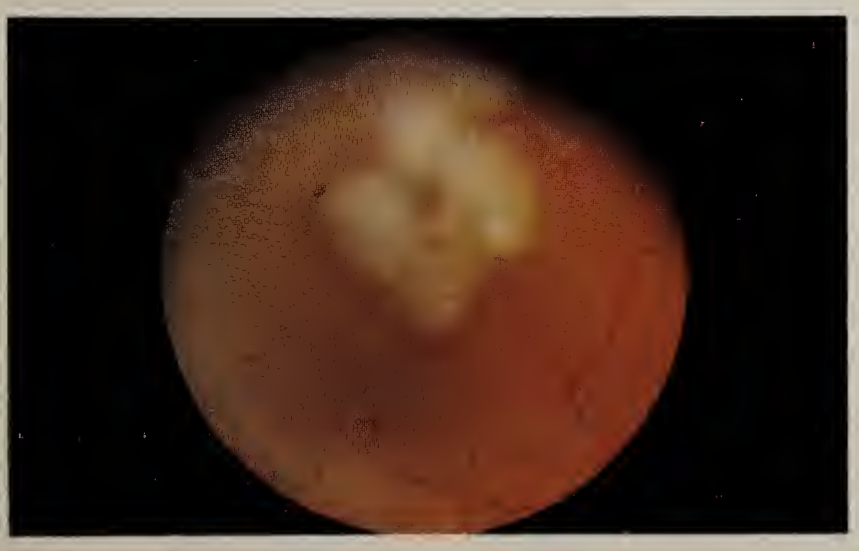

Fig. 12.—Photocoagulation marks immediately after treatment of peripheral retinal tear.

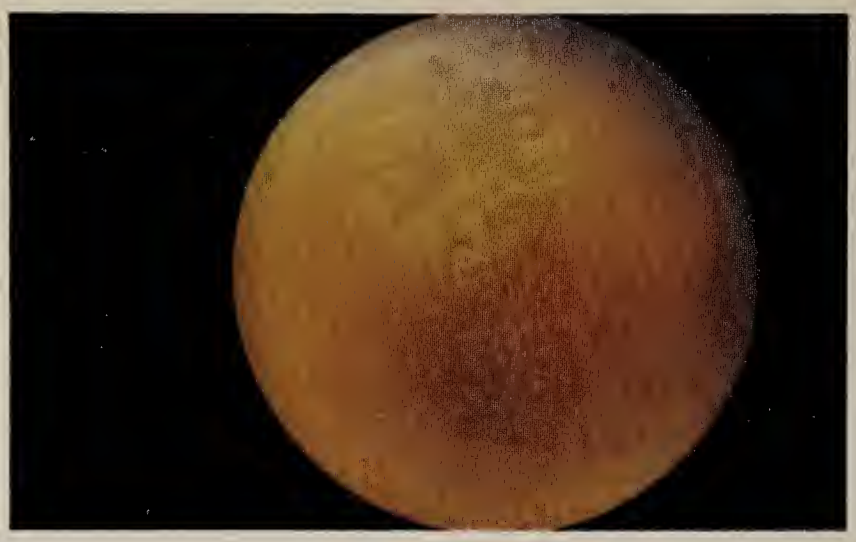

Fig. 13.—Final pigmented seal of tear in Fig. 12.

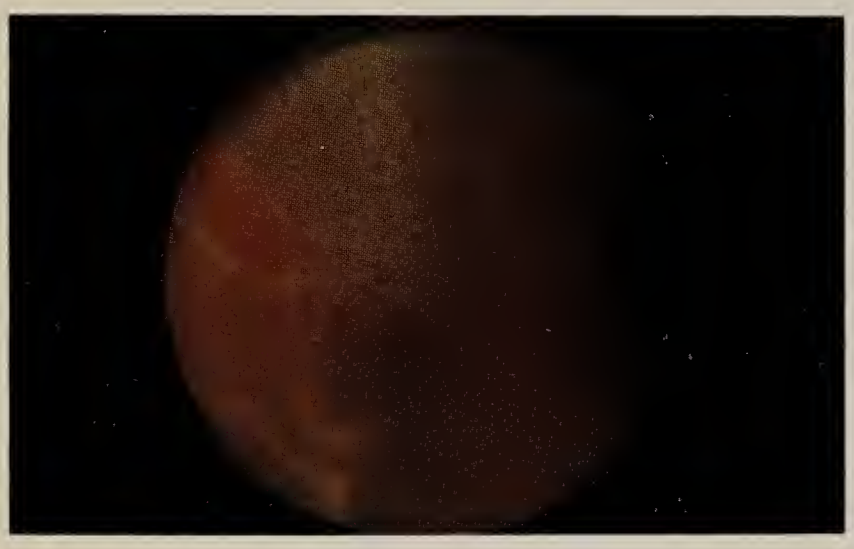

Fig. 14.—Large retinal tear with retinal detachment.

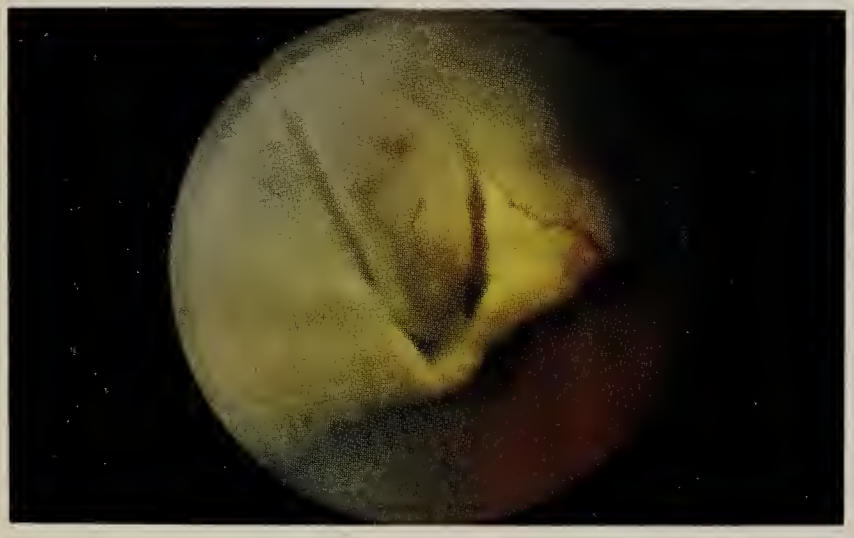

Fig. 15.—Tear postoperatively, treated by diathermy coagulation and silicone buckle.

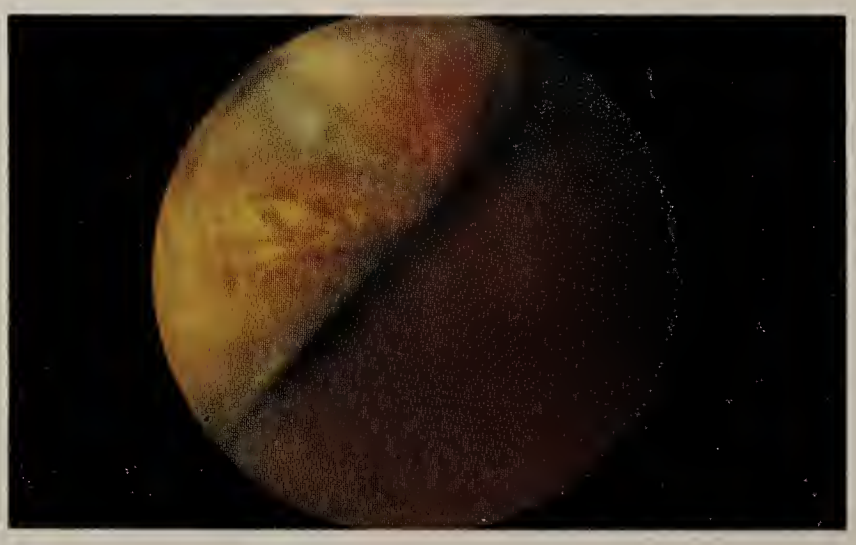

Fig. 16.—Final result of tear in Fig. 5 showing obliterated tear area on silicone buckle.

TOXIC EFFECTS OF CHLOROQUINE ON THE EYE

Norbert J. Nowicki, M.D.[1]

Chloroquine (Aralen) and hydroxychloroquine (Plaquenil) which have found such wide usage in the treatment of rheumatoid arthritis, lupus erythematosus, and other collagen diseases have been found to produce ocular changes some of which are reversible and others of which, unfortunately, are irreversible.

CORNEAL CHANGES

Several investigators[1,2] have reported corneal changes up to one-third of patients on prolonged chloroquine therapy. These changes consist of microscopic white or yellowish fan-shaped opacities which are superficially located on the cornea. These corneal deposits disappear after cessation of therapy with no disturbance of vision and have no apparent pathologic significance.

There are no known ways to indicate which person taking chloroquine will develop the reversible corneal changes or, of particular importance, the irreversible retinal changes due to the ingestion of chloroquine.[3] There have been reports of corneal deposits developing with daily doses of 400 to 500 mg. of chloroquine and disappearing when the dose was reduced to 250 mg. per day. Other patients may require discontinuance of the drug for the corneal deposits to disappear and still other patients regularly using 750 to 1,000 mg. of chloroquine a day fail to develop corneal changes. No correlation has been found between those persons developing corneal deposits due to chloroquine and those developing hemolytic anemia in which there is a deficiency of 6-phosphate dehydrogenase in the peripheral blood.

RETINAL CHANGES

The retinotoxic manifestations of chloroquine have been widely reported in the literature since Hobbs[4] first reported the entity in 1959. The patient so affected first notices impairment of central vision and decreased vision at night. Visual fields reveal central or paracentral scotoma and peripheral constriction. There may be some defect in color vision. Ophthalmoscopically, there is a loss of the normal foveal reflex, degenerative mottling of the macular region by fine pigmentation (Color Plate #10), fine pigmentary degeneration in the peripheral retina, retinal arteriolar narrowing, and increased visibility of the peripheral choroidal vessels. These changes are not unlike those of retinitis pigmentosa.

It may be difficult to correlate the subjective visual complaints with objective signs of retinopathy. The electroretinogram (ERG) usually shows a marked reduction in the photopic and scotopic curves. A pericentral ring scotoma may be demonstrable without any visible retinal pigmentary changes and only generalized arteriolar narrowing evident.[5]

Case Report. This 51 year old white female developed rheumatoid arthritis of hands and knees in 1957. Because of intolerance to salicylates and a previous history of peptic ulcer contraindicating corticosteroids, she was placed on chloroquine 250 mg. b.i.d. from Sept., 1957, until the middle of 1962. At this time she lost central vision in both eyes, and examination at the U. of Michigan revealed bilateral macular degeneration with pigmentation and marked diminution of the B-wave in the ERG. Examination at Presbyterian-St. Luke's Hospital in Aug., 1963, showed corrected vision of 20/200

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in the right eye and 20/300 in the left eye. Both fundi showed slight narrowing of the arteries, fine pigmentary degeneration of the maculas (Color Plate #10) about 1.5 disc diameters in size, and normal retinal periphery. Visual fields showed bilateral central scotomas without peripheral constriction.

The histopathologic changes in chloroquine retinopathy are a destruction of the rods and cones and a marked destructive process in either the outer nuclear layer[6] or inner nuclear layer[7] of the retina. The storage of chloroquine in the melanin-containing tissues of the eye suggests that the pigment epithelium of the retina may be the primary site of cellular damage.

The chloroquine stores in the body are deposited in the liver, heart, spleen, kidney, and lung and have been demonstrated in the plasma, red blood cells and urine of patients as long as five years after the last known ingestion of the drug.[8] This is why cessation of the drug does not necessarily result in cessation of the signs and the progression of the retinotoxicity. An average of at least one year after the discontinuance of chloroquine is necessary for the electroretinographic (ERG) changes to return to normal,[9] if they ever do so.

TREATMENT

Since the characteristic retention of chloroquine may be the cause of the progressive loss of vision that can occur in spite of discontinuing the drug, a therapeutic regimen of acidification of the urine to increase urinary excretion of chloroquine has been suggested. Use of ammonium chloride orally produces a 20% to 80% increase in urinary excretion of chloroquine. Administration of dimercaprol causes a two to three fold increase in chloroquine excretion. This reduction in the body's store of chloroquine may not deplete the ocular stores of chloroquine, but in a patient with retinotoxicity it is certainly worthy of a trial.

Rubin[10] suggests as a therapeutic regimen in chloroquine toxicity the use of ammonium chloride, 8 gm. per day for three days and repeated each week for a minimum of six to eight weeks. Dimercaprol could be used at a recommended dose of 2.5 to 3 mg. per kilogram of body weight administered intramuscularly four to six times a day for the first three days and at 12 hour intervals thereafter for a total of ten days.

Due to the great variability which apparently exists regarding the onset of visual impairment due to chloroquine toxicity, no definite drug-dose retinotoxic relationship has been arrived at, although many men recommend not exceeding a daily dose of 250 mg. of chloroquine. Since the discovery of early signs of toxicity is so important, every patient being placed on long term chloroquine therapy should have a base line ophthalmic examination before initiating therapy and follow-up examinations every three to four months while on the drug.

SUMMARY

Chloroquine and hydroxychloroquine, so widely used now in the management of collagen diseases, have been found to produce toxic manifestations in the eye consisting of reversible corneal deposits and irreversible retinal changes. The signs of retinotoxicity are impaired vision and peripheral and central visual field defects. The retinal changes consist of loss of the foveal reflex, macular pigmentary degeneration, fine pigmentary changes in the peripheral retina and arteriolar narrowing.

Because of the irreversible nature of the retinal changes and the prolonged body storage of chloroquine, frequent visual examinations of patients on prolonged chloroquine administration is suggested. A therapeutic regimen to promote the body's release of stored chloroquine is outlined as a possible method of halting the retinotoxic effects.

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RETINAL DETACHMENT

HOWARD L. WILDER, M.D.[1]

Because retinal detachment surgery has undergone marked changes in the last ten years, it seems worthwhile to write a resume of what is happening and why. The changes that have taken place are those in instruments, of materials, and in techniques.

PATHOLOGIC ANATOMY AND PHYSIOLOGY

The gelatinous vitreous fills the interior of the eye from the lens posteriorly, and this mucopolysaccharide gel with collagen lamellae touches the retina everywhere. An adhesion of the vitreous with the retina from inflammation or degeneration can later produce a tear in the retina if the adherent vitreous strands contract or a sudden movement or trauma dislocates the vitreous.

On the outer side of the retina is the choroid. The deeper layers of the retina containing the visual receptors (rods and cones) depend on the choroid for its blood supply. When the retina is separated from the choroid in retinal detachment, the retina starves and deteriorates. This is why there is an element of urgency in retinal detachments, especially when the central macular area of sharp vision is involved.

On the outer side of the choroid is the sclera, a tough collagenous white wall of the eye so important in all retinal surgery.

Retinal detachments can arise because of defects in any of these four tissues. The vitreous can undergo a process of shrinkage called vitreous retraction, and any pathological attachments of the vitreous to the retina can produce a tear in the retina. The retina itself is capable of undergoing numerous degenerative processes whereby retinal holes or tears form without influence from its neighbors. The choroid may undergo inflammatory or degenerative processes which secondarily weaken the retina. Lastly, the sclera itself may become so thin or stretched as in myopia or ectasias that the retina cannot adapt itself to the enlarging wall without thinning with eventual hole formation.

Whatever the primary cause, most retinal detachments arise because a hole or a tear occurs in the retina. This retinal break allows fluid to pass from the vitreous through the break, separating the retina from the choroid. Depending on the properties of the vitreous, a variable amount of time may elapse between the development of the retinal break and appearance of the retinal detachment. The retinal break can develop without any retinal detachment ever taking place, especially if there are chorio-retinal adhesions already present to seal off the tear. On the other hand, vitreous fluid can flow through the break and produce a retinal detachment within the same day or at any time thereafter. In general, tiny retinal holes in the presence of healthy gelatinous vitreous tend to delay detachment formation because flow of fluid is slower. Conversely, large retinal tears coupled with breakdown of the vitreous gel into fluid tends to produce the detachment very early, frequently within hours or days.

RETINAL BREAKS WITHOUT DETACHMENT

The patient is very fortunate if the diagnosis of a retinal break can be made before the condition progresses to a retinal detachment. Unfortunately however, symptoms of a retinal tear are minimal

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or absent. There may be some "lightning flashes" and fine "floaters" caused by collapse of the vitreous structure and mechanical stimulation of the retina. The greatest and sudden visual loss occurs when a retinal tear ruptures a retinal vessel, producing vitreous hemorrhage. A retinal tear is the single most common cause of a vitreous hemorrhage.

If the patient is fortunate enough to have the diagnosis made in the stage of retinal tear without detachment, the prognosis is excellent. The retina is in contact with the choroid, and the surgeon need only place some form of coagulation in the choroid and edges of the retinal tear to obliterate it by the formation of a scar. The surgeon has used many things to insult the choroid and retina. Many years ago it was the injection of a solution of alkali. Also, diathermy was applied by needles introduced through the sclera and more recently the application of cold through the sclera. Or it may be burning by means of an intense light (photocoagulation) or monochromatic wave length (Laser) introduced through the pupil and absorbed by the pigment of the retinal epithelium and choroid. In cryo-coagulation, a liquid nitrogen probe coagulates the choroid and retina by freezing through the scleral side, and has the advantage over diathermy that it does not produce any permanent change in the sclera itself.

Therapy by photocoagulation, is by the use of a strong beam of visible light, produced by a 3500 watt Xenon bulb and directed by the ophthalmologist with a modified ophthalmoscope through the pupil onto the area of the retinal tear. The light is brought to a focus by the refractive media of the eye, and contact lens if necessary, and is absorbed by the pigment of the retinal epithelium and choroid. Heat is generated by this intense light, similar to focusing of sunlight with a magnifying glass to burn a piece of colored paper. If the retina and choroid are in contact, a chorio-retinal coagulation with subsequent adhesion is produced. The more recently developed Laser ("light amplification stimulated by emission of radiation") works exactly as does photocoagulation but the light source through the ruby crystal is monochromatic and very intense. Thus far Laser therapy is still in the experimental stage, some problems still remaining in regard to regulation of dosage during treatment. At the present time, the viewing apparatus used by the surgeon is superior in diathermy and cryosurgical techniques as compared to those used with light coagulator systems. In the former the surgeon has the advantages of the binocular indirect ophthalmoscope, these being an intense light source combined with a binocular, stereoscopic view of the retina. It may safely be said that the development of this superior instrument for examining the retina has advanced retinal surgery more than any other aid. Unfortunately, the light coagulator systems have not yet been able to develop a binocular indirect ophthalmoscopic viewing system.

Color Plate #11 shows a pigmented chorio-retinal scar at the macula, as a result of photocoagulation of a macular hole to prevent a retinal detachment. This reaction process takes in from ten to twenty-one days. It is true that the pigmented scar produces a scotoma or blind area, but so does the hole that existed prior to therapy. Color Plate #12 shows a typical peripheral retinal tear immediately after photocoagulation. In Color Plate #13, the tear is well sealed off.

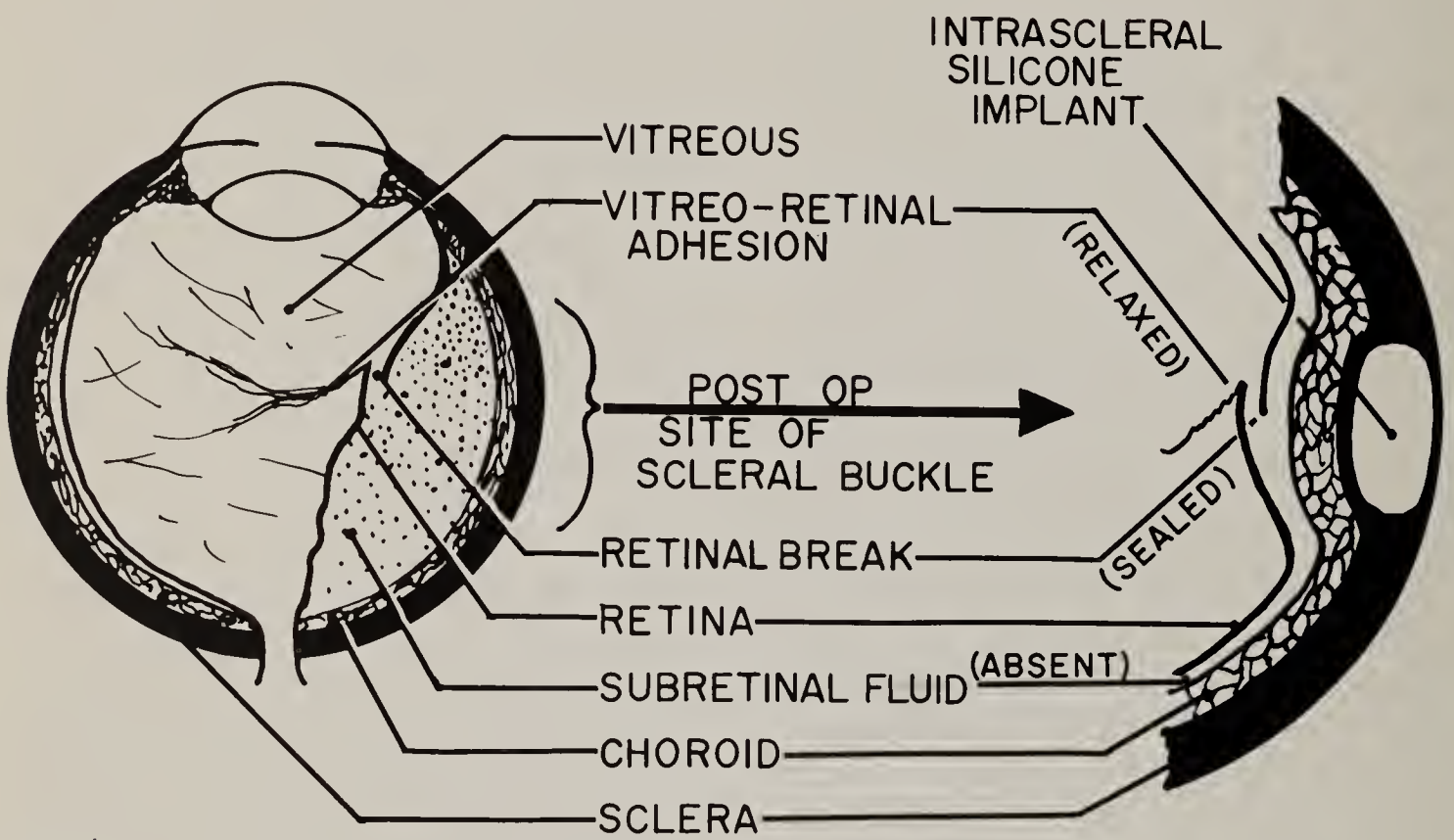
RETINAL DETACHMENT WITHOUT BREAKS

A group of cases exist where the retinal detachment is the result of pathological processes other than have been described above. Retinal tears have occasionally been noted in these cases, but they are not the significant pathology. Malignant melanomas of the choroid push the retina into an elevated position, and later a serous fluid also accumulates under the retina. The important problem here is in diagnostic error, because such an eye should be enucleated and not exposed to retinal surgery. Retinal detachment can be secondary to proliferating tissue in the

vitreous of diabetic retinitis proliferans. This connective tissue is probably induced by vitreous hemorrhages, and the contracting forces in the vitreous pulls the retina off. This vitreo-retinal pathology is non-surgical for the most part. There is a third small group of non-surgical retinal detachments, secondary to rare ocular inflammations or systemic toxic conditions.

TREATMENT OF RETINAL DETACHMENT

If fluid flows through the retinal break and accumulates beneath the retina, separating retina and choroid, the photocoagulator or Laser cannot be used because the retinal tear which must be coagulated and sealed to the choroid, is separated from the choroid by the fluid between these two structures. This is a



(FIG. 1)

true retinal detachment. There is no retinal function corresponding to the detached area, and the patient usually notices a progressive, curtain-like visual field defect opposite the area of detachment. If the macular area of sharp vision becomes detached for a week or more, permanent reduction in central vision may result even after successful surgical reattachment of the retina. Accordingly, early cases of retinal detachment endangering macular vision are considered emergencies.

In the surgery of retinal detachment, it is necessary to drain the subretinal fluid separating retina and choroid to bring these two structures into apposition. True, coagulation is still a necessary part of the procedure to produce a chorio-retinal seal, but the major problem is bringing the parts together and holding them in place. This is accomplished by a procedure termed scleral buckling. Silicone rubber is sutured outside or within the sclera to indent the sclera and produce a buckle in the region of the retinal tear, forcing the retina to fall on this mound of choroid and maintain it in this position. A permanent buckle or hourglass configuration of the eye can be created by the addition of a silicone band that encircles the globe in the region of the equator. The purpose of these buckles produced by silicone is threefold. (1) The silicone is used to produce contact of choroid and retina so that firm chorio-retinal adhesions will form to seal the retinal break. (2) Drainage of subretinal

fluid through a scleral-choroidal incision is facilitated when the volume of the eye is reduced and the ocular pressure increased by the buckle and encircling band. This might be compared to a patient who wears a support under his belt for an umbilical hernia. If he loses 20 pounds about his mid-section, the belt can be tightened or shortened and the supporting element now fuctions properly again. (3) Many detachments have an element of vitreous shrinkage as part of their etiology, and this may be progressive. Inward buckling of the wall of the eye decreases traction of the shrinking vitreous on its retinal adhesion. The mechanical effects of the buckling procedure are illustrated in Fig. 1. The silicone materials are to this date the most inert materials found and are left in place as permanent implants. Recently, preserved homograft sclera has been used to increase the height of the buckle and protect the underlying sclera from internal erosion by the plastic band and pad.

Color plate #14 shows a large retinal tear in the presence of a retinal detachment. Color Plate #15 shows the same tear immediately post-operatively in apposition with the choroid and maintained by a silicone scleral buckling. The tear is well coagulated and sits on the mound produced by the silicone materials. Color Plate #16 shows the same area with the tear obliterated by the pigmented chorioretinal scar which seals the tear.

PROGNOSIS AFTER OPERATION

About 10-15% of retinal detachments cannot be cured by operation, usually because of extensive vitreous retraction or fixed scar tissue in the vitreous or retina. A successful anatomical re-attachment of the retina usually means an improvement in visual field and vision compared with the pre-operative status, but normal central vision may be defective if the macula was previously detached. Patients can be told that the return of function after a retinal detachment is analogous to that after a coronary occlusion. There are many patients who will recover full function, some who recover with limitations in activities and function, and some unfortunate enough not to recover at all.

CATARACTS INDUCED BY DRUGS

William E. Deutsch, M.D.[1]

This paper will largely be concerned with lenticular opacities which can be induced by drugs administered systemically. A large number of drugs have been found to produce cataracts, either as a side effect of therapy, when exposure has been accidental, or when used on experimental animals in the laboratory.[1] (Table 1.) Three of these drugs; dinitrophenol, triparanol, and corticosteroids, will be considered in greater detail.

There is much species specificity with these agents; e.g., triparanol will produce cataracts in man, but not in rats, mice, guinea pigs and rabbits. Corticosteroids even in massive doses fail to produce cataracts in rats. Also, the young of the species are more prone to develop lens changes from these drugs than the adult.[2] There is also a large degree of individual susceptibility to toxic effects from these agents; dinitrophenol was used indiscriminately by hundreds of thousands of people yet only 0.1 to 1% developed cataracts.

MORPHOLOGY OF TOXIC CATARACTS

Experimentally, cataracts induced by toxic agents in laboratory animals first show damage to the epithelial cells at the equator of the lens peripherally, where these cells divide and lay down new lens fibers throughout life. On slit lamp or biomicroscopic examination, small vacuoles appear at the equator and are pushed posteriorly by elongating lens fibers into the posterior subcapsular area. Degenerating lens material may also appear here as granular deposits often with a metallic or iridescent sheen. The noxious agent in the aqueous which bathes the lens may penetrate the lens capsule and directly damage the lens cortex.

Dinitrophenol Cataracts. Of interest in the mid-nineteen-thirties were cataracts produced by the ingestion of dinitrophenol, a chemical which increased metabolic activity and was used for weight reduction without dieting.[4] By 1935, papers began to appear in the medical literature describing toxic symptoms such as skin eruptions, jaundice, agranulocytosis and cataracts. At the insistence of the Federal Food and Drug Administration, "reducing pills" containing dinitrophenol were withdrawn from the market and no new cases of this type of cataract have appeared. The cataracts were all characteristically in the posterior subcapsular area with less severe anterior subcapsular involvement. Other areas of the lens remained relatively clear.

Case #1. This patient (M.K.) was first seen in October 1938, at the age of 25 with the complaint of poor distance vision. Her history revealed the ingestion of reducing pills containing dinitrophenol for six months about three years previously. This had been done under a doctor's supervision. On examination, the patient's best corrected visual acuity was 20/40 in the right eye and 20/80 in the left eye. There were dense central posterior subcapsular whitish opacities. In October, 1939, a needling of the left cataract followed five days later by a lavage of the lens cortex resulted in 20/20 corrected vision. She was not seen

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TABLE 1
DRUGS FOUND TO BE CATARACTOGENIC ON SYSTEMIC ADMINISTRATION
(From Grant[1])

In Man and Animals:	Busulfan (Myleran) Dinitro-o-cresol Dinitrophenol Ergot Galactose
Possibly in Man:	p-Dichlorobenzene Lead Naphthalene Trinitrotoluene
In Animals:	Alloxan Cobalt Decahydronaphthalene Epinephrine Iodoacetate Mimosine (leucenol) Naphthalene beta-Naphthol Tetrahydronaphthalene Thallium

again until 1962, at which time vision in the right eye had fallen to 4/200 due to progression of the anterior and posterior subcapsular lens opacities described 23 years previously. An intracapsular cataract extraction was performed on this eye with recovery of 20/20 vision.

Triparanol Cataracts. In 1960 and 1961, triparanol (Mer-29, W. S. Merrell Co., Cincinnati, Ohio) was used extensively to lower blood cholesterol by inhibiting synthesis of cholesterol in the body. In November, 1961, Medical World News first published an article based on a preliminary report in the Staff Proceedings of the Department of Dermatology of the Mayo Clinic that several patients receiving triparanol had hair, skin and lenticular changes.[5] On December 1, 1961, Merrell sent a letter to all physicians warning of these side effects. Subsequently, the drug was withdrawn from the market.

These four clinic cases and others[6,7,8,2] all having skin changes consisting of dryness and itching, ichthyosis, even exfoliation along with loss of hair, also developed posterior subcapsular cataracts. These have been described as white branching opacities coalescing to form rosettes with a golden sheen. The cataracts developed even after the drug had been discontinued. These findings have led to a large number of lawsuits against the pharmaceutical manufacturer, most of which are still pending.

Case #2. (E.G.) This lady had been followed since 1942 for routine refractions and examinations with corrected vision always of 20/20 in each eye. In August 1961, the only abnormality was mild hypertensive-arteriosclerotic retinal changes. She returned in June of 1962, at the age of 62, complaining of blurred distance vision, especially in the right eye. She gave a history of taking Mer-29 from February to December 1961. Vision in the right eye was reduced to 20/40 and in the left eye to 20/35 because of multicolored vacuoles and opacities in the posterior subcapsular area of both lenses. Within the next two years, the right cataract became completely opaque and was extracted uneventfully. The left cataract has shown no progression in almost three years.

Corticosteroid Cataracts. Of equally widespread interest at about the same time were reports of posterior subcapsular lens opacities in 5 of 22 patients with rheumatoid arthritis treated with 10 to 16 mg. or more of prednisone daily for one year or more.[9-13] These cases showed no correlation with other factors such as age or severity of the rheumatoid arthritis, and, in the control group not receiving steroids, no patients developed lens changes. These cataracts were all described as consisting of small white crystalline opacities, separated by small vacuoles with an iridescent sheen and located entirely in the posterior subcapsular area. Not all patients had sufficient opacification to be aware of symptoms, and very few had significant visual reduction. On questioning, the patients usually admitted to symptoms of photophobia and increase in glare disturbance.[12] Patients receiving large doses of corticosteroids for prolonged times for such conditions as lupus erythematosis, nephrosis and bronchial asthma were studied and showed similar lens findings. It has not yet become clear whether reduction of dosage or stopping the drug

will halt the progress of the lenticular changes.

There is considerable discrepancy in the literature concerning the prevalence of steroid cataracts. Various series have produced different percentages of patients developing cataracts. Some of these differences are doubtless due to the criteria used in determining what constitutes a cataract. There is fairly widespread agreement that the factors of large dosage and prolonged exposure enhance the probability of lenticular change.

There have also been several reports of the topical application of steroids in the eye producing lenticular opacities. This is in addition to the well substantiated observations of topical steroids producing glaucoma. However, most of these cases had serious corneal or intraocular pathology, or were of an age at which the causal relationship is open to doubt.[14-15]

Case #3 (R.C.) This 58 year old school teacher was treated for rheumatoid arthritis for many years; receiving steroid injections in the affected joints in 1950, and varying dosages of several steroid preparations from early 1962 to the present. I first saw this patient in April 1964 because her vision had become increasingly blurred for the previous fourteen months. Vision was reduced in the right eye to 20/60 and in the left eye to 20/80 because of posterior subcapsular lens opacities, appearing as glistening vacuoles centrally and grey opacities throughout this area. There were similar, though less dense, changes in the anterior subcapsular region. During the past year, these cataracts have progressed moderately.

Differential Diagnosis of Toxic Cataracts. As in case #3, there is some difficulty in the differentiation of toxic cataracts from other types. The common senile cataract may start with posterior subcapsular opacities, but they usually do not have the iridescent coloring of toxic cataracts. Also, nuclear sclerosis and peripheral cortical opacities may indicate the likelihood of the cataract being senile in type. A true diabetic cataract is rare, characterized by vacuoles and snow-flake opacities in the anterior subcapsular area. Cataracts are frequently secondary to other ocular conditions such as uveitis, trauma, pigmentary degeneration of the retina, or radiation. Cataracts may be associated with diseases such as atopic dermatitis, hypoparathyroidism and the congenital myotonic degenerations. Clinically, these cataracts may be impossible to differentiate from the toxic type, but the history and clinical findings associated with the primary condition usually help to establish the diagnosis.

COMMENT

In this litigation-minded age, we are sometimes asked to give a definite answer as to whether a certain drug has caused cataracts in a specific patient. This may not be difficult in a young individual receiving a cataractogenic agent (case #1). However, what about the young patient with atopic dermatitis who is treated with corticosteroids? If a cataract develops, is it due to the atopic dermatitis or the corticosteroids? In individuals over 40 years of age, the possibility of senile cataracts always complicates the diagnosis of toxic cataracts (cases #2 & 3). Patient #2 was well into the age of predilection for senile cataracts, but was known to have no lens changes prior to the ingestion of the toxic drug. Interestingly, in her case, one cataract progressed to complete maturity while that in the fellow eye remained stationary. In case #3 the cataracts may have been due to the poorly understood senile process, or may have been caused or hastened in both intensity and time by the oral corticosteroids. The problem is even more complicated if the corticosteroid therapy, either systemically or locally, is given for the treatment of an ocular condition which, in itself, might cause cataracts. Only by animal experimentation, and carefully controlled statistical studies in patients can the iatrogenic effects of drugs be ascertained.

The physician must be aware of the side effects of drugs. However, he must also avoid condemning a valuable therapeutic agent as harmful before sufficient evidence is analyzed. When all the dangers of a valuable drug such as the corticosteroids are known, and its therapeutic worth weighed against its danger, the physician should not be forced to withhold the medication if the beneficial effects are more important than the potential hazards.

SUMMARY AND CONCLUSION

The hazard of producing cataracts is one of the side effects of any ingested chemical agent with which we come in contact. This must be considered in the careful clinical evaluation of any proposed drug. Care must be taken that the agent itself is the cataractogenic factor and not just an associative contributor. Three established cataractogenic agents have been described with case histories to demonstrate and possibly clarify some of the difficulties in the study of toxic cataracts.

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STEROID GLAUCOMA

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Elevation of intraocular pressure produced by the local or systemic administration of the cortico-steroids has been generally recognized since 1962[1], although sporadic reports had appeared in the ophthalmic literature since 1953[2–6]

CLINICAL FEATURES

Glaucoma induced by steroids strongly resembles open angle glaucoma (chronic simple glaucoma) in many ways. In spite of the increased intraocular pressure the eye appears entirely normal externally and there are no symptoms. The angle of the anterior chamber remains open without visible evidence of an outflow block, but the outflow facility* is reduced (Fig. 1). The facility is improved and the intraocular pressure lowered by the common antiglaucomatous medications. Finally, if the pressure persists for a sufficient period, glaucomatous atrophy of the optic nerve and associated field loss will occur.

Steroid glaucoma differs from open angle glaucoma (chronic simple glaucoma) primarily because the elevation of intraocular pressure and reduced facility of outflow are completely reversible at any time by stopping the steroids. Also the pupil is often enlarged, the upper lid may droop, and the cornea may increase in thickness.

The frequency of intraocular pressure rise after local or topical administration of steroids is startlingly high[7-9]. In a series of normal individuals with negative family histories of glaucoma and negative water provocative tests**, approximately thirty per cent developed a mean rise of 4.6 mm. Hg. (13.6 to 18.2)*** in conjunction with a decreased facility of outflow from 0.30 to 0.21[7]. The remaining 70 per cent of this group developed insignificant rises in pressure. When the offspring of known glaucomatous patients were tested seventy-five per cent responded significantly, and in patients with known open angle glaucoma the significant response was almost one hundred per cent. These glaucoma patients developed a steep rise in mean pressure from 17 to 32 mm. Hg., with a marked fall in outflow facility from a mean of 0.21 to 0.09.

*The outflow facility is a term applied to the quantity of aqueous humor which can flow through the trabecula into the canal of Schlemm (Fig. 2). It is determined by the functional test, "Tonography," which consists of artificially raising the intraocular pressure by the weight of the tonometer and recording the change in intraocular pressure for a given period of time. (See Fig. 1.) The resultant micro liters of aqueous expressed per mm. of Hg. per minute equals the facility of outflow. The normal facility is considered greater than 0.15, whereas less than 0.13 is considered definitely less than normal.

**Water Provocative Test consists of the ingestion of one liter of water within ten minutes on a fasting stomach. An elevation of the ocular tension of six or more mm. of Hg. is considered suggestive of open angle glaucoma.

***Normally 16-22 mm. Hg.

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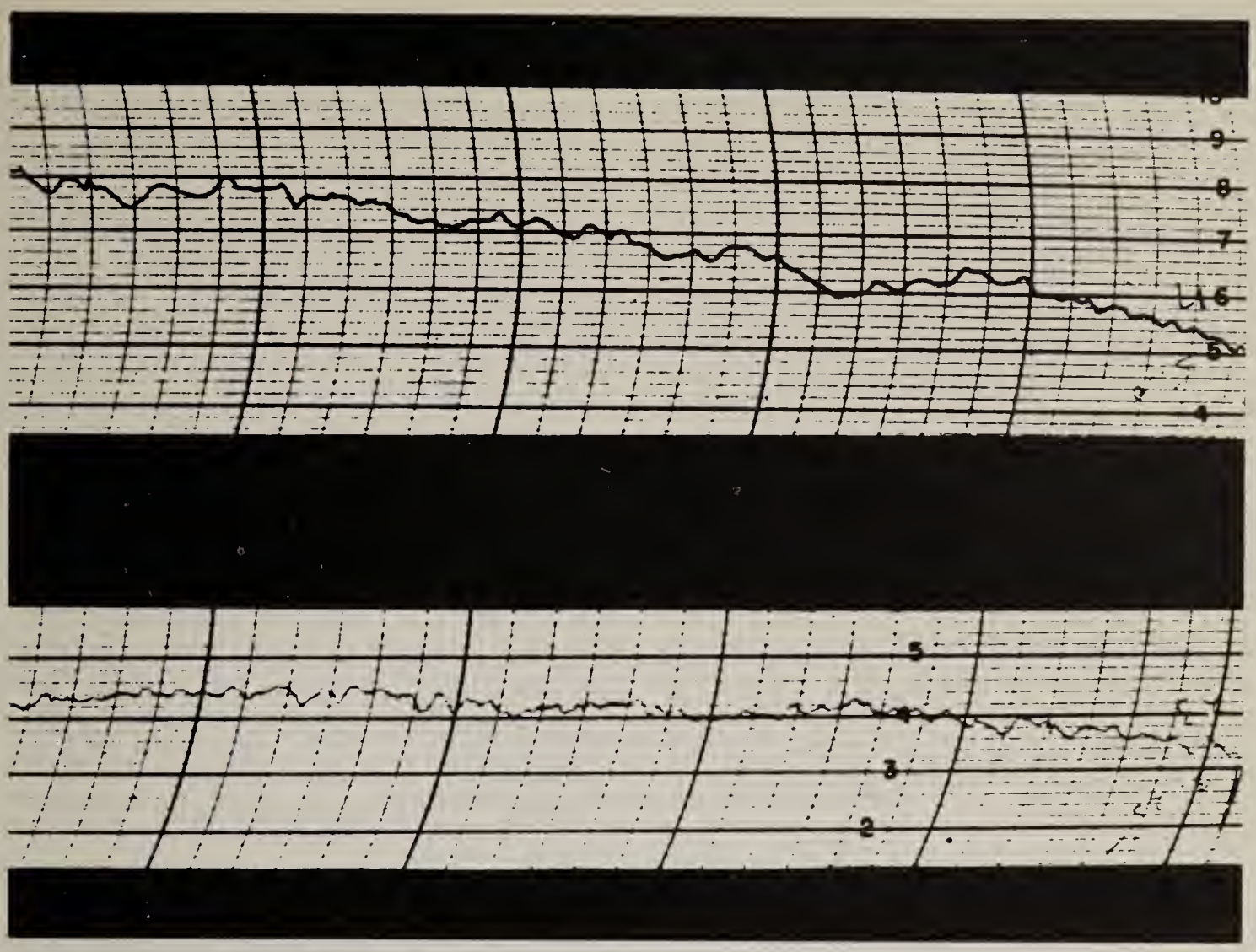

Fig. 1—Tonogram from right eye of patient with steroid glaucoma. The upper tracing reveals an intraocular pressure of 23 mm. Hg. and a facility of outflow of 0.13 microliters/min./mm. Hg. with patient using topical steroids.

The lower tracing taken one month after cessation of steroids reveals an intraocular pressure of 17 mm. Hg. and a facility of outflow of 0.30 microliters/min./mm. Hg., or a complete return to normal values.

Systemic administration of the corticosteroids produces less consistent responses, which may be due to less drug reaching the anterior segment of the eye. However, in a study of 48 patients on oral steroid therapy, of at least 25 mg. of cortisone or its equivalent a day for at least six months, a small but statistically significant increase of tension and a decrease in facility of outflow occurred[10]. Ten patients developed pressures above normal, and the effect was greater the longer the steroid was used. In a control series of similar patients not on steroids, these findings did not occur.

ETIOLOGY

The mechanism by which outflow facility is reduced with subsequent elevation of intraocular pressure is unknown. Several hypotheses have been offered.

1. Systemic retention of water. Substantial water intake reduces the osmotic pressure of the blood, and more fluid is drawn into the tissues of the body, including the eye.[11] This will temporarily elevate the pressure within the eye. Steroids, however, decrease sodium excretion through the kidney, resulting in an increase in extracellular fluid with change in osmotic pressure. The theory that steroid glaucoma is produced by this method seems inadequate because the newer steroids have minimal sodium retention effect but still elevate the intraocular pressure and local adminstration produces a more consistent rise, suggesting that the mechanism is located within the eye.

2. Local water retaining factors. Thickening of the cornea has been associated with steroid glaucoma, but not in

parallelism with tension elevation.[12] This may be a result of alteration in the corneal endothelium, and if the steroid should also affect the trabecular endothelium, the pore size of the trabecula could be reduced with a decrease in outflow facility (Fig. 2.).

3. Steroid action on mucopolysaccharides. A hyaluronidase-sensitive mucopolysaccharide has been demonstrated in the spaces or pores of the trabecular meshwork in the adult normal eye[13-15] and in glaucoma. That these mucopolysaccharides contribute to outflow resistance is suggested by the increased outflow facility that follows the removal of this substance by hyaluronidase[16].

Cortisone produces a degeneration of the mast-cells, presumably liberating mucopolysaccharides or their components.[17]

If the steroids should release mucopolysaccharides within the eye, and if they accumulate within the trabecular spaces, a decreased facility of outflow and increased intraocular pressure might reasonably result.

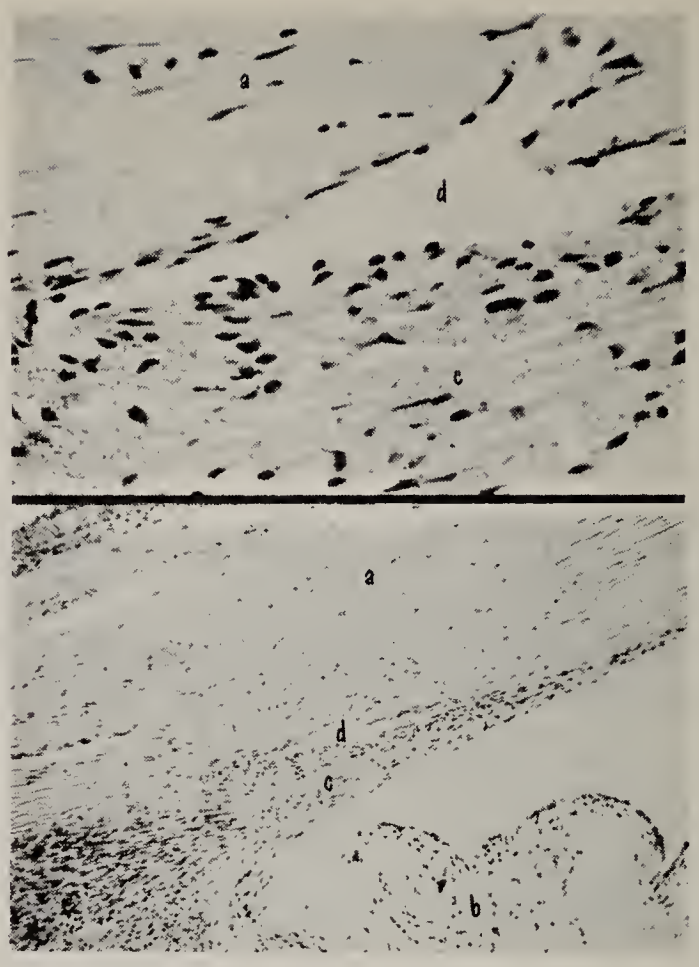

Fig. 2—Cross section of the angle of the anterior chamber revealing the anatomy of the outflow mechanism. A. The cornea; B. the iris; C. the trabecula, and D. the Canal of Schlemm.

In the lower figure the trabecula is shown in high power revealing the so called "pores."

PRACTICAL AND THEORETICAL CONSIDERATIONS

Irregardless of mechanism, steroid glaucoma is a phenomena of considerable practical and theoretical significance.

GENETIC SIGNIFICANCE

Previously, it was noted that almost one hundred per cent of open angle glaucoma patients develop a steep rise in tension after the intensive use of local steroids, that seventy-five per cent of the offspring of glaucoma patients develop a rise and thirty per cent of apparently normal individuals show a small but significant rise. In a hereditary study where the individuals received instillations of 0.1% betamethasone Q.I.D. for 3-6 weeks, Becker and Hahn demonstrated that patients with chronic simple glaucoma behaved as if they were homozygous for the steroid responsive state (gg)[18 19]. The offspring of the glaucoma population as well as the moderate responders to the steroid were classified as the heterozygous responsive or carrier state (ng). Those individuals with no or little response were labelled the homozygous normal state (nn).

Furthermore, if with the compilation of additional data the response can be quantitated, it may be possible to distinguish the carrier state (ng) of this recessive gene from the normal state (nn) purely on the basis of steroid responsiveness[20]. This would enable the ophthalmologist to diagnose open angle glaucoma years before it develops, as well as genetically advising carriers of their status. The importance of this is self evident.

SURGICAL APPLICATION

In post-operative situations calling for an increased intraocular pressure, topical steroids can be used. This is particularly helpful in antiglaucomatous procedures where artificial outflow channels are created.

RESEARCH POTENTIAL

(1) A possible endocrine control of intraocular pressure is suggested since steroids elevate the pressure and epinephrine lowers it. Progesterone is also known to lower the pressure.

(2) Since open angle glaucoma seems to be genetically predetermined, a search for the possible enzyme system, or other system could have wide significance.

(3) Steroid glaucoma can be investigated in rabbits[21] since the mechanism is also effective in them.

CLINICAL IMPORTANCE

Obviously, care should be used in treating known glaucoma patients with steroids, either topically or systemically[22] all patients requiring long-term steroid therapy should have routine eye examinations.

SUMMARY

The local, and to a much less extent, systemic administration of corticosteroids can induce glaucoma with many of the clinical features of open angle glaucoma (chronic simple glaucoma). It is, however, completely reversible after the cessation of the steroids. The elevated intraocular pressure is due to a decrease in the facility of outflow of aqueous from an unknown cause. This abnormal responsiveness to steroids is transmitted as a recessive hereditary characteristic, and hopefully can be used to detect preglaucoma and carriers without glaucoma. Some practical applications of this information are presented.

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TREATMENT OF OCULAR INJURIES

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During the past several years, there have been some advances in the recognition and treatment of certain ocular injuries. Some of these will be selected for discussion on the basis of frequency, need for recognition and emergency management by the general physician or surgeon, or because of new methods of treatment by the ophthalmologist.

LACERATIONS OF THE LID MARGIN

Some of the deformity of a through and through laceration involving the lid margin can be reduced by taking special precautions during the initial repair. These include: (1) measures to prevent notching of the lid margin; (2) measures to prevent a scar which has a great tendency for contracture if it involves both surgical layers of the lid; i.e., the outer skin and orbicularis muscle layer, and the inner supporting tarsal layer; and (3) measures to prevent a long vertical scar.

In order to anticipate and compensate for later notching of the tarsal margin of the lid as scar develops, an elliptical excision of the tarsus can be performed at the time of the inital repair. This produces an initial outward puckering to compensate for a tendency to later notching (Fig. 1a & b.) Another method to promote more secure closure of the tarsal lid margin consists of a tongue and groove closure, in which the tarsus is split on one side and sharpened into a wedge on the opposite side with closure by a mattress suture (Fig. 2). Years ago, John Wheeler applied the carpenter's principle of secure joining of two ends of a piece of wood by the halving technique; i.e., by removing the inner half of each piece and overlapping the ends. This can be done on the lid, considering the skin and tarsus as the two halves. However, because of the elasticity of the skin, it is probably unnecessary to excise any tarsus or eyelashes. Instead, the skin can be excised on one side and a skin flap pulled over the incision to prevent a through and through wound (Fig. 3). A long vertical laceration through the lid can later result in downward traction and eversion of the lid, resulting in exposure of the eye and tearing. A Z-plasty can be performed at the time of the initial repair to eliminate the vertical scar and also anticipate later shrinkage of the tissues by producing vertical elongation. However, unless the vertical laceration is sufficiently long (e.g., 1 inch) a Z-plasty may produce more additional scarring and defeat its purpose (Fig. 4a & b).

[1]Attending Ophthalmologist, Chairman, Department of Ophthalmology, Presbyterian-St. Luke's Hospital. Clinical Professor of Ophthalmology, University of Illinois.

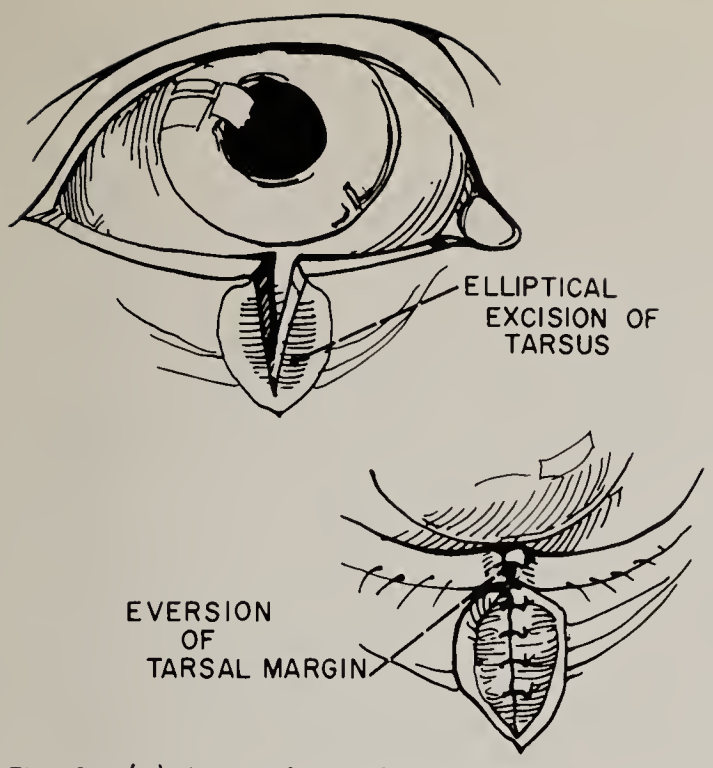


Fig. 1—(a) Area of tarsal resection.
(b) Close of elliptical defect in tarsus, producing an outward puckering of the tarsal margin. Separate closure of skin over this.

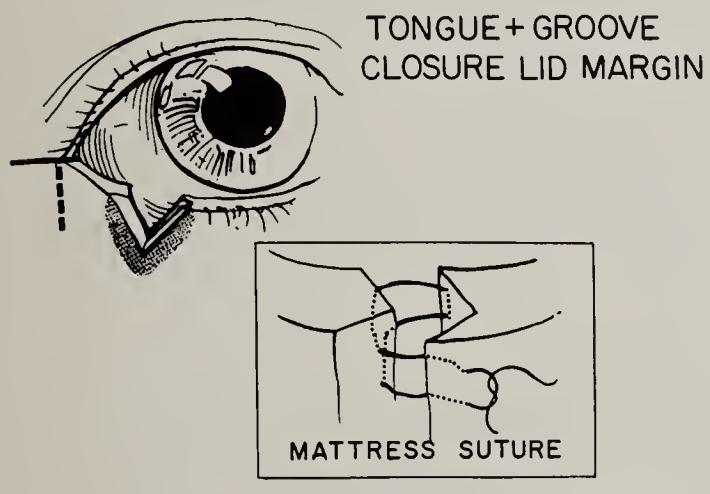


Fig. 2—Tongue and groove closure of the tarsal lid margin with a mattress suture. Horizontal canthotomy incision through skin, and subcutaneous severing of the inferior portion of the lateral canthal ligament unnecessary unless there is loss of tarsal tissue.

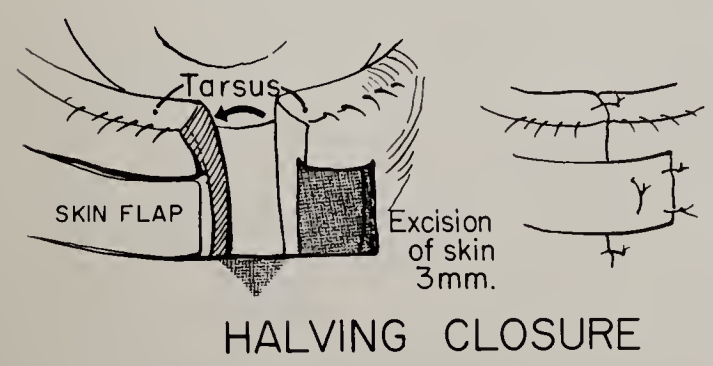


Fig. 3—Modified halving closure of laceration through both skin and tarsal layers of lid margin.

BLOW-OUT FRACTURES OF THE FLOOR OF THE ORBIT

During the past several years, it has been recognized more frequently that a blunt injury to the eyeball can cause a depression fracture of the floor of the orbit without necessarily causing serious damage to the eye (Fig. 5)[1]. Orbital fat can herniate into the antrum, resulting in enophthalmos. Also, the important diagnostic sign of inability to look upward is caused by incarceration of the inferior rectus muscle within the fracture or into the antrum (Fig. 6.) In the so-called *traction test*, local anesthetic is instilled and the eye cannot be passively rotated upward by forceps. An X-ray, Waters' view or laminagram, usually but not always shows a fracture of the floor of the orbit with protrusion of soft tissue into the antrum. If the clinical diagnostic features are present, surgical intervention is indicated as soon as possible, even if the X-ray is inconclusive or negative. This is usually done by a team of an otolaryngologist or plastic surgeon with an ophthalmologist. At the Presbyterian-St. Luke's Hospital, many of these cases have been performed by Drs. Stanton A. Friedberg and William Deutsch. Briefly, the technique consists of the following: (1) a horizontal incision through the skin to the rim of the orbit; (2) elevation of the periosteum well back behind the rim until the blow-out fracture becomes visible; (3) a Caldwell-Luc incision into the antrum to push up the tissues into the orbit; (4) repair of large defects with a bone graft obtained from the anterior antral wall, or possibly some of the newer plastics such as Marlex, Teflon, or Nylon sheets or mesh placed under the periosteum through the orbital incision and fashioned to fit the orbital floor; (5) secure closure of the periosteum over the anterior orbital rim; and (6) packing of the antrum with vaseline gauze to support the fracture. Treatment within a week after injury gives the best results, although improvement can be obtained if surgery has been delayed for as long as several months after injury.

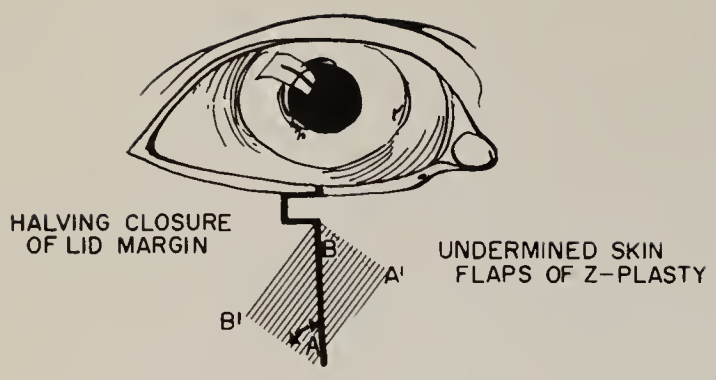
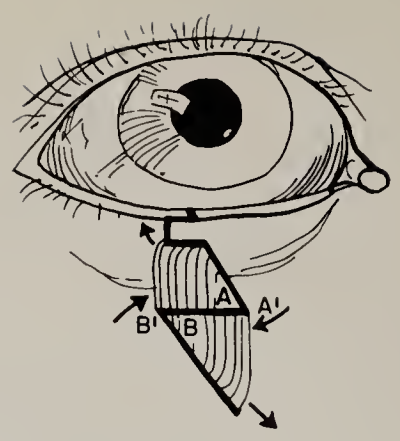


Fig 4—(a) Skin incisions and undermining of triangular flaps in preparation for Z-plasty repair of long vertical laceration through lower lid.



(b) Transposition of flaps, eliminating vertical wound and protruding vertical lengthening.

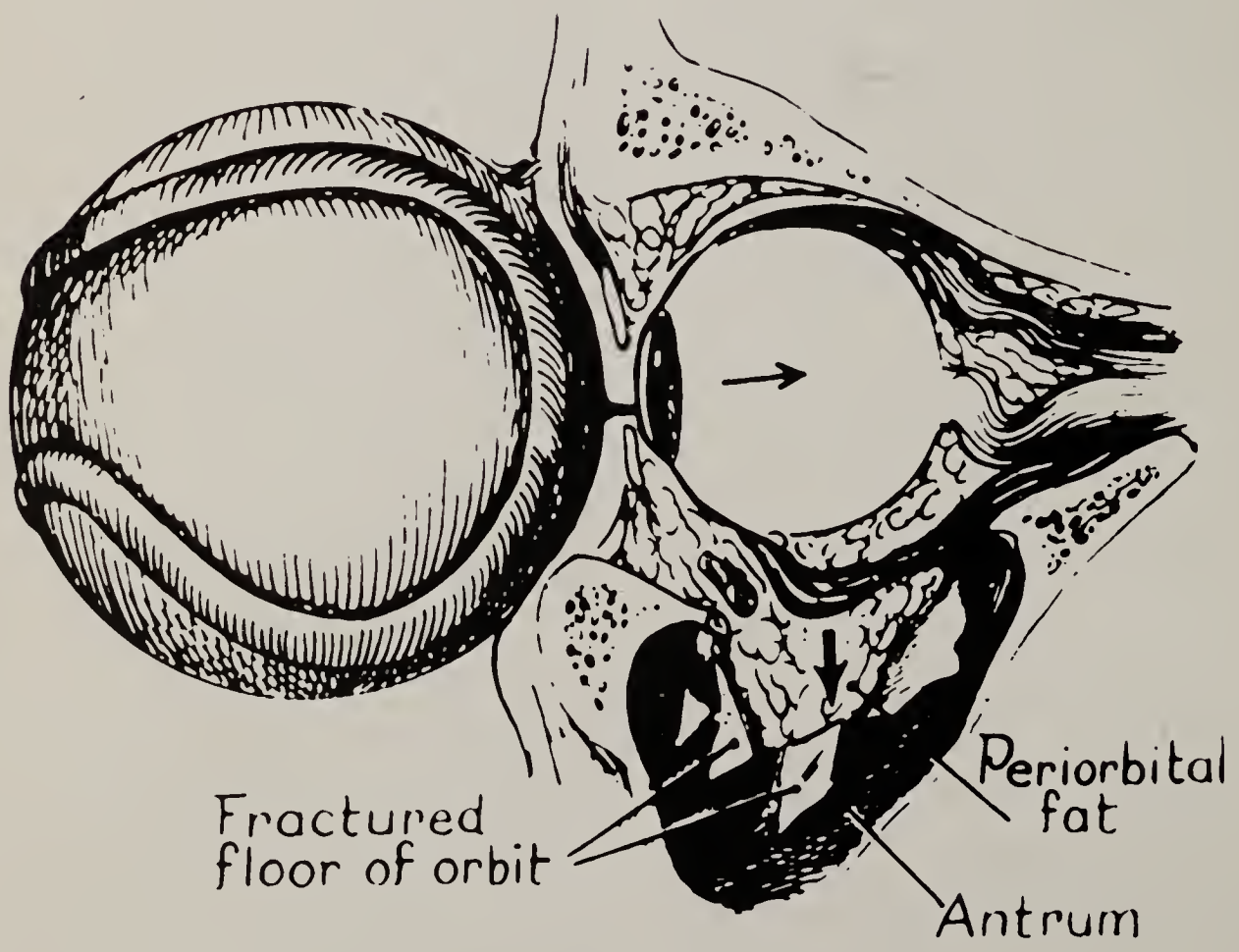


Fig. 5—Blunt injury to eye, producing blow-out fracture of the orbital floor with incarceration of inferior oblique and inferior rectus muscles in the antrum (Courtesy of Converse and Smith[1]).

Fig. 6—(left)—Patient with blowout fracture of left orbit. Upward gaze before operation. Note fixity of left eye. (right)—Same patient after operation. Note position of affected eye in upward gaze, demonstrating release of incarcerated inferior rectus muscle. (Courtesy of Converse, J. M., and Smith, B.: Tr. Am. Acad. Ophth. 64:676-688, Sept.-Oct., 1960.)

ANTERIOR CHAMBER HEMORRHAGE FOLLOWING BLUNT INJURY

An apparently mild blunt injury to the eyeball can produce hemorrhage into the anterior chamber, probably arising from torn vessels at the root of the iris. The inital hemorrhage may be slight or may even reabsorb, to be followed two to four days later by a more severe recurrent hemorrhage of more serious prognostic significance. Erythrocytes can be absorbed intact through pores of the trabeculum,[2] or may disintegrate and be phagocytyzed by macrophages and iris cells. The most serious complication is elevation of the intraocular pressure or secondary glaucoma, usually associated with a so-called "8-ball" hemorrhage filling the anterior chamber with dark clotted blood. The glaucoma is probably caused by hemorrhagic debris and pigment-laden macrophages which fill the anterior chamber angle and block the filtering trabeculum.[3] An anterior chamber filled with blood combined with glaucoma leads to the deposition of blood pigment in the cornea or so-called blood staining of the cornea, which may require many months to clear.

Treatment of Anterior Chamber Hemorrhage. Even a small anterior chamber hemorrhage from blunt injury should be considered an ocular emergency. If possible, the patient should be hospitalized with complete bed rest and binocular eyepads for 4 to 5 days. Pilocarpine 2% may be instilled once a day to help open up the trabeculum and provide a greater surface of the iris for absorption of blood, in addition to reducing the likelihood of glaucoma. Every 3-7 days, it is probably desirable to

dilate the pupil with Homatropine 2-5% or Cyclogyl 1% to prevent posterior synechias which might develop because of traumatic iritis. A carbonic anhydrase inhibitor such as Diamox to reduce the formation of aqueous is probably desirable; 250 mg., 2-4 times a day. If an 8-ball hemorrhage persists for several days and secondary glaucoma develops up to a tension of 40-50 mm. Hg., intravenous urea has been recommended.[4] Such cases usually require irrigation of the anterior chamber with a solution of fibrinolysin (Thrombolysin), a proteolytic enzyme prepared commercially by exposing high concentrations of purified profibrinolysin from human plasma to an activator substance, purified streptokinase. Briefly, this technique has been described by Scheie et al[5]: (1) introduction of a thin-walled 19 gauge blunted needle through a shelving corneal incision; (2) flushing out the anterior chamber and breaking up the blood clot using a freshly-made solution (1250 units/cc) of fibrinolysin in 5% dextrose. Usually not more than 50,000 units of material is necessary to break up the clot in 5-90 minutes. Another potent activator of fibrinolytic mechanisms is urokinase obtained from human male urine used in doses of 5,000 to 25,000 units.[6]

TRAUMATIC RECESSION OF THE ANGLE OF THE ANTERIOR CHAMBER

In 1963, Wolff and Zimmerman from the Armed Forces Institute of Pathology described a contusion deformity of the angle of the anterior chamber in which the ciliary body becomes split and reattaches itself farther posteriorly.[7] This can be detected soon after the injury by examination of the angle of the anterior chamber through a contact lens (gonioscopy), a deepening of the anterior chamber and apparent retrodisplacement of the root of the iris being visible. If this has occurred over an area greater than 240°, the patient should be examined for many years in case a symptomless open angle type of glaucoma develops. This type of glaucoma can be controlled medically in many cases, otherwise a filtering operation is necessary.[8] One follow-up study of patients with anterior chamber hemorrhage showed that 71% had angle recession, 11% developed glaucoma within 3 years, none between 3-10 years, and 20% of 20 cases followed over 10 years.[9] Trabecular damage therefore is present early or becomes significantly compromised as the patient becomes older. It has also been found that traumatic dislocation of the lens may be associated with recession of the angle and glaucoma.[10] Treatment therefore is directed towards control of the glaucoma rather than extraction of the lens, unless a cataract is producing an inflammatory reaction.

PERFORATING INJURIES

Direct perforation of the globe can occur from any missile, and the globe can also rupture at the weakest spots from a blunt injury; e.g. at the corneo-scleral junction or in the thin part of the sclera posterior and beneath the recti muscles. After a perforating injury in the anterior ocular segment, the iris usually prolapses and appears as a black nubbin either directly exposed or beneath the conjunctiva. Such a prolapsed iris acts as a plug against further leakage of aqueous, and occasionally a physician futilely attempts to wipe off this apparent black "foreign body". This situation represents an ophthalmologic emergency, because delay in surgical repair increases the incidence of several post-traumatic complications, including; (1) purulent infection; (2) sympathetic inflammation or uveitis of the opposite normal eye; and (3) glaucoma, due to adhesions of the iris to the filtering trabeculum. Accordingly, the physician who sees the injured patient should not forcibly examine such an eye for fear of further extrusion of intraocular contents, but apply eyepads to both eyes, administer prophylactic antibiotics, and refer the patient immediately

to an ophthalmologist for hospitalization and surgery. Surgery consists of excision of the prolapsed iris and resuturing of the wound directly with special 6-0 or 7-0 silk, or 6-0 catgut sutures. Subconjunctival injection of antibiotics should be routinely given in such cases at the close of operation; e.g., 100,000 to 500,000 units of soluble penicillin with 20,000 to 50,000 units of streptomycin, preferably with some adrenalin to prolong the high concentration of antibiotic in the eye for 48 hours. The visual prognosis after perforating injury becomes progressively worse when the lens is damaged producing a cataract, if the laceration is large, or if an intraocular foreign body is present.

Sympathetic Ophthalmia or Uveitis. Unlike a purulent intraocular infection caused by pyogenic organisms introduced at the time of injury, a low-grade inflammation in the uveal tissue (iris, ciliary body, and choroid) can persist or develop even after several months. Uveitis can also be caused by a toxic or allergic effect of lens protein from a traumatic cataract. If repair of the prolapsed iris has been delayed or especially if the iris is exposed, sympathetic ophthalmia can develop in both the injured and uninjured eye after 10 to 14 days, and usually within the first 6 months after injury. This dreaded complication occurs in less than ½% of perforating injuries. If the injured eye is enucleated within 10 days after injury or before sympathetic ophthalmia has developed in the normal eye, the uninjured eye does not become involved. Accordingly, it is safe to wait for 10 days after injury and after repair of the wound to determine: (1) whether the injured eye shows persistent intraocular inflammation; and (2) whether there is potentially useful vision in the injured eye. The ophthalmologist must therefore decide before 10 days whether the risk of sympathetic ophthalmia is greater than the chances of obtaining useful vision in the injured eye. If so, enucleation of the injured eye is indicated immediately. Sympathetic ophthalmia is probably a combination of virus infection which has not yet been demonstrated, plus allergy to uveal pigment which has been demonstrated. However, prophylactic use of corticosteroids does not reduce the incidence of this complication. Enucleation of the injured eye after the onset of sympathetic ophthalmia in the other eye does not improve the prognosis. If bilateral inflammation has already developed, at times the vision in the injured eye is eventually better than that of the opposite eye. Treatment consists of the intensive and long-term use of systemic steroids, with the majority of such patients retaining useful vision.

INTRAOCULAR FOREIGN BODIES

Space does not permit detailed discussion of the management of intraocular foreign bodies. However, every case of perforating injury of the eye should have an X-ray to rule out a radio-opaque intraocular foreign body. If two separate X-rays are taken with the eye in different positions, the intraocular foreign body will move if it is located in the eye, unless it is exactly in the center of rotation of the eye. It will also move if caught in the sclera or the adjacent external tissues of the eye. Non-radio-opaque foreign bodies in the anterior segment of the eye can be detected by using a dental film placed against the side of the nose and rotating the eye medially. Exact localization of the foreign body to facilitate removal can be done by: (1) direct observation with the ophthalmoscope if the media are clear, and scleral indentation at operation with a diathermy probe while viewing the fundus with an ophthalmoscope; (2) reference to radio-opaque objects placed in front of or on the eye according to the technique of Sweet or the Comberg contact lens containing lead dots; and (3) use of the Berman electromagnetic localizer at the time of operation, placed at the point of the sclera nearest the foreign body. Iron foreign bodies should be localized accurately and removed before they destroy vision by degenerative siderosis in the retina and other

TABLE 1

CLASSIFICATION
CHEMICAL BURNS OF THE EYES

NON-PROGRESSIVE:	*ACIDS* (EXCEPT HF, H_2SO_3 or SO_2, AND ACIDS CONTAINING HEAVY METALS).	
PROGRESSIVE:	*ALKALIES:*	LIME (CaO) LYE (NaOH or KOH) AMMONIA (NH_4OH)

VESICANT WAR GASES: e.g., MUSTARD, N-MUSTARD, LEWISITE
OTHERS: HF, SO_2, CHROMIC, *LIQUID LACRIMATORS,* INDELIBLE DYES.

IRRITANT: *LACRIMATORS,* E.G., CHLORACETOPHENONE.

TABLE 2

EMERGENCY TREATMENT OF CHEMICAL BURNS OF THE EYE

1. Immediate copious lavage with any bland fluid, preferably normal saline.
2. Removal of solid particles of corrosive, using local anesthetics if nec.
3. Instillation of neutralizing agents: repeatedly for 15 min. then q. 1-2 hrs. for 24 hrs.: e.g.,
   Vs. Acid Burns: 1% sod. bicarbonate
   Vs. Alkali Burns: Acetate Buffer pH 4.7

Glacial acetic acid	2.9 cc (0.05 Molar)
Sodium acetate.3 H_2O	6.8 Gm (0.05 Molar)
Dist. Water q.s.	1000.0 cc

   Vs. Lime: 2% disodium versenate
4. Cold compresses.

TABLE 3

LATER TREATMENT OF CHEMICAL BURNS AFTER 24 HOURS

1. Vs. Iritis: mydriatics such as homatropine 2% or Cyclogyl 1% once a day.
2. Vs. Inflammation, Vacularization, and Infection: combination of steroid and antibiotic instilled into eye q.i.d.: e.g., a solution of
   Metimyd (prednisolone 0.1% and sulfacetamide 10%)
   Neo-Delta-Cortef (prednisolone 0.25% and neomycin 0.5%)
   Neo-Hydeltrasol (prednisolone 0.5% and neomycin 0.5%)
   Neo-Decadron (dexamethasone 0.1% and neomycin 0.5%)
3. Possibly a lamellar corneal transplant for severe necrosis or imminent perforation.
4. Vs. symblepharon: mucous membrane grafts.

ocular tissues. In general, magnetic foreign bodies in the posterior segment of the eye are removed with a magnet through a scleral incision nearest the foreign body, or anteriorly through a safer area of the pars plana of the ciliary body.

CHEMICAL BURNS OF THE EYES

Chemical burns of the eyes can be classified as non-progressive, progressive and irritant (Table 1). This does not mean that prolonged exposure to a strong acid cannot destroy the cornea and vision, but that the prognosis of the injury can

be judged more accurately after an acid burn than after a progressive alkali burn. Treatment of chemical burns can be outlined as follows (Table 2, 3). It is far more important to wash out the eye vigorously with any sort of bland fluid or water immediately after the contact with the corrosive than for the individual to wait until seen by the physician for more elaborate irrigations. Vigorous lavage is more important than the use of neutralizing solutions, and care must be taken to remove all solid particles of corrosive which might have become embedded in the conjunctiva beneath the upper lid. A local anesthetic such as Ophthaine ½% often facilitates adequate irrigation and relieves pain, but local anesthetics should not be used as treatment thereafter because of induced delay in healing. Sodium versenate 2% can be used for 15 minutes after lime burns as an eye bath, then every 1 to 2 hours for 24 hours.[11] In sporadic reports[12] and a few personal cases, the initial burn has seemed so severe that necrosis of the corneal and scleral tissue with perforation seemed likely. In such cases, the necrotic tissue has been removed and replaced with a lamellar corneal transplant. In three personal cases, the eye has been saved and in one case useful vision obtained, but there has been a serious problem in proper healing of the graft at the necrotic edges of the host cornea or sclera. Corneal transplantation for late chemical burns, which are severely scarred with little clear corneal tissue and much vascularity, has a very poor prognosis. Unfortunately, the Cardona plastic implant being performed in New York City is not well retained in this type of severe chemical burn.

HEAT BURN OF THE CORNEA

In 1963, Dr. John W. Curtin and I cared for a man who had been severely burned in an airplane crash. The lids were quite necrotic and after many split-thickness grafts, adequate protection of the globe and cosmetic result were obtained by Dr. Curtin. The unusual aspect of this case was that the man apparently had such a will to live that he kept his eyes open while running through the flames, resulting in heat burns of both corneas. This rare complication of burns was so severe in the left eye that the cornea perforated within 10 days without much evidence of inflammatory infiltration or infection. A large 8 mm. penetrating corneal transplant was performed, crossing over into scleral tissue with a full iridectomy beneath this. This graft remained clear for several months with vision of 20/50. Unfortunately, however, a homograft reaction set in and this resulted in clouding of the graft. A second graft was performed about a year later, healed poorly and became cloudy. The right eye showed only a mild heat burn of the lower ⅓ of the cornea on admission to the hospital. However, observation revealed that the corneal stroma became thinner and thinner as if it were melting away. Accordingly, a conjunctival flap was pulled over the lower ½ of the cornea which halted the process and vision in this eye two years later was 20/30+.

SUMMARY

The management of certain types of ocular injuries has been discussed briefly, emphasizing those aspects which might be of greater interest to the general physician and surgeon and some aspects where new treatments are available.

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THE EDITOR'S PAGE

It is a worthwhile stimulus for a specialized department to be invited by the Editor of the Medical Bulletin to present an entire issue on a somewhat hybrid branch of medicine for individuals in other specialties. With such a challenge, members of the ophthalmological department were forced to take time to decide what might be significant advances in this specialty, and which work would be of general interest and practicality to other physicians.

A joint research project with the Dept. of Microbiology on the relatively common infection of the cornea by herpes simplex virus resulted in the first published work tempering enthusiasm for the therapeutic value of the much-heralded "specific antiviral agent," idoxuridine. Local and systemic use of corticosteroids can not only induce but also aggravate such herpes simplex keratitis, and these miracle hormones can also induce a reversible glaucoma in individuals with such a recessive hereditary trait or even cataracts after prolonged use. Prolonged use of chloroquine can result in reversible corneal opacification, and retinal damage with permanent loss of vision. A small series of selected patients with severe progressive diabetic retinopathy and vascular proliferans have had hypophyseal stalk sections performed at this hospital, and these results have been evaluated with suggestions for the rather stringent indications when considering this operation. Much experimental work on homograft reactions has been performed in connection with corneal transplantations which have been done successfully for over 30 years. This work has been reviewed, and a case is presented in which the corneal homograft was rejected in spite of intensive use of steroids, but later responded well to the use of the immuno-suppressive agent, azathioprine (Imuran), under the close supervision of medical consultants who are using this drug experimentally. The use of new surgical methods including silicone has made most cases of retinal detachment operable, with an average 80-90% chance of success. Because of the importance of detection of symptomless open angle glaucoma in 2% of adults over 40 years of age, tonometric screening of patients by the general physician during routine examination is important. Emergency surgical treatment of angle-closure glaucoma (acute congestive) must be performed to prevent rapid loss of vision. Because emergency treatment of ocular injuries often comes initially into the hands of the general physician or surgeon, it was considered worthwhile to include a summary of these measures.

It is hoped that this material will be of some interest and use to readers of the Medical Bulletin. The eye is photogenically attractive, and much more can be learned from illustrations in color which have been so liberally permitted in this issue.

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Special Editor
Symposium on "The Eye"